Environment Canada
Health Canada
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Santé Canada

Canadian Environmental Protection Act, 1999

PRIORITY SUBSTANCES LIST ASSESSMENT REPORT

N-Nitrosodimethylamine (NDMA)

Canada

Canadian Cataloguing in Publication Data

Priority substances list assessment report:
N-nitrosodimethylamine (NDMA)

(Priority substances list assessment report)
Issued also in French under title: *Liste des substances d'intérêt prioritaire, rapport d'évaluation, la N-nitrosodiméthylamine (NDMA)*
At head of title: *Canadian Environmental Protection Act.*
Co-published by Health Canada.
Includes bibliographical references.
Issued also on the Internet.
ISBN 0-662-29137-9
Cat. no. En40-215/53E

1. Dimethylnitrosamine — Toxicity testing — Canada.
2. Dimethylnitrosamine — Environmental aspects — Canada.
3. Environmental monitoring — Canada.
I. Canada. Environment Canada.
II. Canada. Health Canada.
III. Series.

TP247.P74 2000 363.738'4 C00-980304-1

Additional information can be obtained at Environment Canada's Web site at www.ec.gc.ca or from the Inquiry Centre at 1-800-668-6767.

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Canadian Environmental Protection Act, 1999

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Environment Canada
Health Canada

September 2001

102-04683/

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List of Acronyms and Abbreviations

ARET	Accelerated Reduction/Elimination of Toxics
CAS	Chemical Abstracts Service
CEPA	*Canadian Environmental Protection Act*
CEPA 1999	*Canadian Environmental Protection Act, 1999*
CFC	chlorofluorocarbon
CTV	Critical Toxicity Value
DMA	dimethylamine
EC_{50}	median effective concentration
EEV	Estimated Exposure Value
ENEV	Estimated No-Effects Value
EPI	Exposure Potency Index
ETS	environmental tobacco smoke
GWP	Global Warming Potential
K_{ow}	octanol/water partition coefficient
kg-bw	kilogram body weight
LC_{50}	median lethal concentration
LCL	lower confidence limit
LD_{50}	median lethal dose
NDMA	*N*-nitrosodimethylamine
ODP	Ozone Depletion Potential
POCP	Photochemical Ozone Creation Potential
PSL	Priority Substances List
PSL2	Second Priority Substances List
TD_{05}	Tumorigenic $Dose_{05}$; dose causing a 5% increase in tumour incidence over background

SYNOPSIS

N-Nitrosodimethylamine (NDMA) is the simplest dialkylnitrosamine, with a molecular formula of $C_2H_6N_2O$. There are no industrial or commercial uses of NDMA in Canada. NDMA is released to the Canadian environment as a by-product and contaminant from various industries and from municipal wastewater treatment plants. Major releases of NDMA have been from the manufacture of pesticides, rubber tires, alkylamines and dyes. NDMA has also been detected in drinking water and in automobile exhaust. Sources of release of NDMA may occur across Canada, but releases have been quantified only in Ontario. NDMA may also form under natural conditions in air, water and soil as a result of chemical, photochemical and biological processes.

Photolysis is the major removal pathway from surface water, air and land. However, in surface waters with high concentrations of organic substances and suspended matter, photodegradation is much slower. In subsurface water and in soil, biodegradation is the removal pathway of importance. NDMA is unlikely to be transported over long distances in air or to partition to soil and sediments. Because of its solubility and low partition coefficient, NDMA has the potential to leach into and persist in groundwater. It is metabolized and does not bioaccumulate. NDMA is generally not detectable in surface waters, except for localized contamination from industrial sites, where end-of-pipe effluent concentrations as high as 0.266 µg/L have been measured.

Acute and chronic toxicity data are available for aquatic organisms. The most sensitive toxic effect was a reduction in the growth of algae at 4000 µg/L. Concentrations of NDMA in Canadian surface waters are less than the threshold for adverse effects estimated for aquatic organisms. No data on concentrations of NDMA in sediments or in soil have been identified in Canada. NDMA is not involved in stratospheric ozone depletion and is not an important contributor to climate change or photochemical smog formation.

NDMA has not been detected in ambient air, except in the vicinity of industrial sites, in small surveys of several cities in southern Ontario. Low concentrations of NDMA have been measured in drinking water in Ontario, where sources have included the contamination of groundwater with industrial effluents and the formation of NDMA in water treatment plants. The presence of NDMA has been demonstrated in some foods in Canada, most frequently in beer, cured meat and fish products, and some cheeses, although levels of NDMA have decreased in these products in recent years owing to changes in food processing. Some of these changes have been mandated under the Canadian *Food and Drugs Act* and Regulations.

Based upon laboratory studies in which tumours have been induced in all species examined at relatively low doses, NDMA is clearly carcinogenic, with a very strong likelihood that the mode of action for the induction of tumours involves direct interaction with genetic material. Qualitatively, the metabolism of NDMA appears to be similar in humans and animals; as a result, it is considered highly likely that NDMA is carcinogenic to humans, potentially at relatively low levels of exposure.

Based on the information available, it is concluded that NDMA is not entering the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity, or that constitute or may constitute a danger to the

environment on which life depends. NDMA is considered to be entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health. Therefore, NDMA is considered to be "toxic" as defined in Section 64 of the *Canadian Environmental Protection Act, 1999* (CEPA 1999).

While there have been a number of measures taken to limit exposure of the general population in Canada to NDMA in foodstuffs, cosmetics and consumer products, recent data on the NDMA content of foodstuffs and rubber-containing products in Canada other than infant feeding bottle nipples and pacifiers have not been identified. Moreover, with the exception of monitoring conducted in Ontario in the early 1990s, potential for exposure to NDMA in the vicinity of point sources in Canada is also largely unknown, although stakeholders under the voluntary Accelerated Reduction/Elimination of Toxics (ARET) program have committed to reducing total emissions of NDMA from 6000 g in 1993 to 87 g by the year 2000.

Continued monitoring of levels of nitrosamines (including NDMA) in Canadian foodstuffs to verify reduction of content seems warranted. Determination of the potential presence of nitrosamines (including NDMA) in rubber products other than infant feeding bottle nipples and pacifiers may also be warranted, particularly for those products with which infants (who exhibit mouthing behaviour) may come into contact.

On the basis of limited information from short-term monitoring surveys of ambient air and water near industrial facilities, the priority for investigation of options to reduce exposure to NDMA in the vicinity of such point sources is considered high. It is recommended, therefore, that there be additional investigation of the magnitude of exposure of populations in the vicinity of point sources to assist risk management actions.

Optimization of drinking water treatment to minimize formation of NDMA is also recommended, though such measures must not compromise human health protection.

Since NDMA may be released directly to the environment through the application of certain pesticides, the levels of this nitrosamine in products regulated under the *Pest Control Products Act* should also continue to be monitored. Monitoring by the Pest Management Regulatory Agency has shown that the review standard of 1 µg/g is rarely exceeded.

Owing to the common practice in Canada of applying sewage sludge to agricultural lands and the potential for uptake by plants, it is recommended that concentrations of NDMA in such sludge be monitored to determine the potential of this practice to contribute to the exposure of humans and non-human organisms.

Since NDMA is likely to be carcinogenic to humans at relatively low levels of exposure and is not currently used in commerce in Canada, it is recommended that the manufacture, import and use of the substance be banned in order to prevent its introduction into the Canadian market.

1.0 INTRODUCTION

The *Canadian Environmental Protection Act, 1999* (CEPA 1999) requires the federal Ministers of Environment and of Health to develop and publish a Priority Substances List (PSL) that identifies substances, including chemicals, groups of chemicals, effluents and wastes, that may be harmful to the environment or constitute a danger to human health. The Act also requires both Ministers to assess these substances and determine whether they are toxic as defined in Section 64 of the Act, which states:

> a substance is toxic if it is entering or may enter the environment in a quantity or concentration or under conditions that
>
> (a) have or may have an immediate or long-term harmful effect on the environment or its biological diversity;
>
> (b) constitute or may constitute a danger to the environment on which life depends; or
>
> (c) constitute or may constitute a danger in Canada to human life or health.

Substances that are assessed as toxic as defined in Section 64 may be placed on Schedule I of the Act and considered for possible risk management measures, such as regulations, guidelines, pollution prevention plans or codes of practice to control any aspect of their life cycle, from the research and development stage through manufacture, use, storage, transport and ultimate disposal.

Based on initial screening of readily accessible information, the rationale for assessing NDMA provided by the Ministers Expert Advisory Panel on the Second Priority Substances List (Ministers Expert Advisory Panel, 1995) was as follows:

> NDMA is used in rubber formulations and in the organic chemical industry. The general population is exposed to the substance from ambient air; from foods, including beer, cured meats, fish, and cheeses; from smoking and chewing tobacco; from cosmetic products, including shampoos, conditioners, and children s bath products; from the interior air of automobiles as a result of NDMA use in upholstery and rubber products; and from various household products. There are already steps to minimize exposure to this potent carcinogen from some specific sources including food, cosmetics, pesticides and rubber nipples. However, there are also public health concerns about potential airborne exposure. Moreover, most assessments have not considered the general public s exposure from all sources. An assessment is required to determine the extent of exposure and the associated risks to human health and the environment in Canada.

Descriptions of the approaches to assessment of the effects of Priority Substances on the environment and human health are available in published companion documents. The document entitled Environmental Assessments of Priority Substances under the *Canadian Environmental Protection Act*. Guidance Manual Version 1.0 March 1997 (Environment Canada, 1997a) provides guidance for conducting environmental assessments of Priority Substances in Canada. This document may be purchased from:

> Environmental Protection Publications
> Environmental Technology Advancement Directorate
> Environment Canada
> Ottawa, Ontario
> K1A 0H3

It is also available on the Internet at www.ec.gc.ca/cceb1/ese/eng/esehome.htm under the heading "Guidance Manual." It should be noted that the approach outlined therein has evolved to incorporate recent developments in risk assessment methodology, which will be addressed in future releases of the guidance manual for environmental assessments of Priority Substances.

The approach to the assessment of effects on human health is outlined in the following publication of the Environmental Health Directorate of Health Canada: "*Canadian Environmental Protection Act* — Human Health Risk Assessment for Priority Substances" (Health Canada, 1994), copies of which are available from:

Environmental Health Centre
Room 104
Health Canada
Tunney's Pasture
Ottawa, Ontario
K1A 0L2

or on the Environmental Health Directorate publications web site — www.hc-sc.gc.ca/ehp/ehd/catalogue/bch.htm. The approach is also described in an article published in the *Journal of Environmental Science and Health — Environmental Carcinogenesis & Ecotoxicology Reviews* (Meek *et al.*, 1994). It should be noted that the approach outlined therein has evolved to incorporate recent developments in risk assessment methodology, which are described on the Environmental Substances Division web site (www.hc-sc.gc.ca/ehp/ehd/bch/env_contaminants/psap/psap.htm) and which will be addressed in future releases of the approach paper for the assessment of effects on human health.

The search strategies for identification of data relevant to assessment of potential effects on the environment (prior to August 1998) and on human health (prior to August 1999) are presented in Appendix A. Review articles were consulted where appropriate. However, all original studies that form the basis for determining whether NDMA is "toxic" under CEPA 1999 have been critically evaluated by staff of Environment Canada (entry and environmental exposure and effects) and Health Canada (human exposure and effects on human health).

Almost all of the environmental information was incorporated into the Assessment Report, and therefore no supporting document for the environmental assessment of NDMA was prepared. Sections of the Assessment Report related to the environmental assessment of NDMA were prepared by the following members of the Environmental Resource Group, established by Environment Canada to support the environmental assessment of NDMA:

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Environmental sections of the Assessment Report were also reviewed by the following people: R. Chénier (Environment Canada), G. Moore (Health Canada), A. McLarty (Ontario Ministry of the Environment), E. McBean and J. Kochany (Conestoga-Rovers & Associates) and D. Carlisle (Brez-Carlisle Inc.). Special acknowledgement is given to the following staff of the Ontario Ministry of the Environment for their assistance: L. MacDonnell, B. Birmingham, G. Rutherford, R. Angelow, D. Spry and S. Abernethy.

The content of the health-related sections of this Assessment Report and supporting documentation was prepared by the following

staff of Health Canada, based, in part, on background information compiled by BIBRA Toxicology International (1997, 1998):

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M. Walker

In order to address primarily adequacy of coverage, sections of the supporting documentation pertaining to human health were reviewed externally by B. Birmingham (Ontario Ministry of the Environment) and R. Brecher (Globaltox International Consultants, Inc.).

Accuracy of reporting, adequacy of coverage and defensibility of conclusions with respect to hazard characterization and dose–response analysis were considered at a panel meeting of the following members, convened by Toxicology Excellence for Risk Assessment (TERA) on August 12, 1999, in Ottawa, Ontario:

M. Bogdanffy, DuPont Haskel Laboratory
J. Christopher, California Environmental Protection Agency
M. Dourson, TERA
S. Felter, Procter & Gamble
J. Mandel, Exponent
R. Rudel, Silent Spring Institute
V. Walker, New York State Department of Health

The health-related sections of the Assessment Report were reviewed and approved by the Health Protection Branch Risk Management meeting of Health Canada.

The entire Assessment Report was reviewed and approved by the Environment Canada/Health Canada CEPA Management Committee.

A draft of the Assessment Report was made available for a 60-day public comment period (February 19 to April 19, 2000) (Environment Canada and Health Canada, 2000). Following consideration of comments received, the Assessment Report was revised as appropriate. A summary of the comments and their responses is available on the Internet at:

www.ec.gc.ca/cceb1/eng/final/index_e.html

The text of the Assessment Report has been structured to address environmental effects initially (relevant to determination of "toxic" under Paragraphs 64(a) and (b)), followed by effects on human health (relevant to determination of "toxic" under Paragraph 64(c)).

Copies of this Assessment Report are available upon request from:

Inquiry Centre
Environment Canada
Main Floor, Place Vincent Massey
351 St. Joseph Blvd.
Hull, Quebec
K1A 0H3

or on the Internet at:

www.ec.gc.ca/cceb1/eng/final/index_e.html

Unpublished supporting documentation on the health-related effects of NDMA, which presents additional information, is available upon request from:

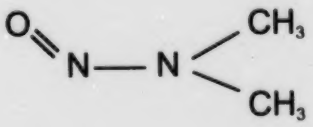
Environmental Health Centre
Room 104
Health Canada
Tunney's Pasture
Ottawa, Ontario
K1A 0L2

2.0 Summary of Information Critical to Assessment of "Toxic" under CEPA 1999

2.1 Identity and physical/chemical properties

N-Nitrosodimethylamine, or NDMA, is the simplest dialkylnitrosamine, with a molecular formula of $C_2H_6N_2O$ and a molecular weight of 74.08 g/mol (ATSDR, 1989) (Figure 1). NDMA belongs to a class of chemicals known as *N*-nitroso compounds, characterized by the *N*-nitroso functional group (–N–N=O), and to the family of nitrosamines, which, in addition, possess an amine function (–NR_2, where R is H or an alkyl group). NDMA is also known as dimethylnitrosamine, dimethylnitrosoamine, *N*,*N*-dimethylnitrosamine, *N*-methyl-*N*-nitrosomethanamine, *N*-nitroso-*N*,*N*-dimethylamine, DMN and DMNA. NDMA has the Chemical Abstracts Service (CAS) registry number 62-75-9.

Figure 1 Chemical structure of NDMA



NDMA is a volatile, combustible, yellow, oily liquid. It is susceptible to photolytic breakdown due to its absorption of ultraviolet light (Sax and Lewis, 1987). The physical/chemical properties relevant to the environmental fate of NDMA are presented in Table 1. The conversion factor for NDMA in air is 1 ppm = 3.08 mg/m^3.

2.1.1 Analytical methods

Analytical methods for NDMA incorporate a concentration step, followed by chromatographic separation of the components in the extract and detection of the *N*-nitrosamine. Concentration steps include liquid–liquid extraction and solid-phase extraction. Chromatographic separations have been achieved almost exclusively by gas chromatography. Detection of NDMA has been accomplished by flame ionization detectors (Nikaido *et al.*, 1977), nitrogen–phosphorus detectors (U.S. EPA, 1984), the Hall electrolytic conductivity detector operated in the reductive mode (von Rappard *et al.*, 1976; U.S. EPA, 1984), the thermal energy analyser or chemiluminescent nitrogen detector (Fine *et al.*,

Table 1 Physical and chemical properties of NDMA

Physical/chemical property	Value[1]
Melting point (°C)	–50
Boiling point (°C)	151–154
Log K_{ow}	–0.57
Vapour pressure	1080 Pa (25°C)
Henry's law constant	3.34 Pa·m^3/mol (25°C)
Solubility	miscible

[1] Includes experimental and calculated values listed in Callahan *et al.* (1979); Clayton and Clayton (1981); ATSDR (1989); Budavari *et al.* (1989); OME (1991); DMER and AEL (1996).

1975; Fine and Rounbehler, 1976; Webb *et al.*, 1979; Kimoto *et al.*, 1981; Parees and Prescott, 1981; Sen and Seaman, 1981a; Sen *et al.*, 1994; Tomkins *et al.*, 1995; Tomkins and Griest, 1996) and mass spectrometry. Mass spectrometric methods have utilized electron ionization low-resolution mass spectrometry (Sen *et al.*, 1994), high-resolution mass spectrometry (Taguchi *et al.*, 1994; Jenkins *et al.*, 1995), chemical ionization tandem mass spectrometry on an ion trap mass spectrometer (Plomley *et al.*, 1994) and laser ionization time-of-flight mass spectrometry (Opsal and Reilly, 1986). Liquid chromatography has also been used in conjunction with a photolysis reactor and (electrospray ionization) mass spectrometry (Volmer *et al.*, 1996). Detection limits range from 0.150 µg/L using nitrogen–phosphorus detectors (U.S. EPA, 1984) to 0.002 µg/L using a gas chromatograph–thermal energy analyser (Kimoto *et al.*, 1981; Tomkins *et al.*, 1995; Tomkins and Griest, 1996) to 0.001 µg/L using gas chromatography–high-resolution mass spectrometry (Taguchi *et al.*, 1994; Jenkins *et al.*, 1995). Comparable detection limits are possible with chemical ionization tandem mass spectrometry on an ion trap mass spectrometer (Plomley *et al.*, 1994).

2.2 Entry characterization

2.2.1 Production, uses and importation

There are no industrial or commercial uses of NDMA in Canada. NDMA is not imported into Canada and is not listed on the Domestic Substances List (Environment Canada, 1996a). In the past, NDMA was used in Canada and other countries in rubber formulations as a fire retardant and in the organic chemical industry as an intermediate, catalyst, antioxidant, additive for lubricants and softener of copolymers (ATSDR, 1989; Budavari *et al.*, 1989).

2.2.2 Sources and releases

2.2.2.1 Natural sources

NDMA can be formed as a result of biological, chemical or photochemical processes (Ayanaba and Alexander, 1974). It may form in water, air and soil by a chemical reaction between ubiquitous, naturally occurring precursors classified as nitrosatable substrates (secondary amines) and nitrosating agents (nitrites) (OME, 1998a). For example, NDMA may form in air during nighttime as a result of the atmospheric reaction of dimethylamine (DMA) with nitrogen oxides (Cohen and Bachman, 1978). Soil bacteria from various precursor substances, such as nitrate, nitrite and amine compounds, may also synthesize NDMA (ATSDR, 1989). NDMA precursors are widespread throughout the environment, occurring in plants, fish, algae, urine and feces (Ayanaba and Alexander, 1974).

2.2.2.2 Anthropogenic sources

NDMA is produced as a by-product of industrial processes that use amines and nitrites under a range of pH conditions. This is due to its inadvertent formation in industrial situations when alkylamines, mainly DMA and trimethylamine, come into contact and react with nitrogen oxides, nitrous acid or nitrite salts, or when trans-nitrosation via nitro or nitroso compounds occurs (ATSDR, 1989). Therefore, NDMA may be present in discharges of such industries as rubber manufacturing, leather tanning, pesticide manufacturing, food processing, foundries and dye manufacturing and, as a result, in sewage treatment plant effluent. Almost all of the releases to the Canadian environment are to water. A regulatory limit for effluents, which was subsequently reduced to 200 ng/L, was introduced in Ontario in 1992, following detection of NDMA in groundwater in Elmira that was contaminated by effluents from a chemical production facility (Jenkins *et al.*, 1995).

NDMA can be also formed during the treatment of drinking water (OME, 1994a); it has also been detected in emissions from diesel vehicle exhaust (Goff *et al.*, 1980).

NDMA may form directly in sewage as a result of the biological and chemical transformation of alkylamines in the presence of nitrite (Ayanaba and Alexander, 1974; ATSDR, 1989). It may also be released into the environment as the result of land application of sewage sludge containing this compound (Pancholy, 1978; McBean, 1999).

NDMA's precursor, DMA, together with nitrite, may enter surface water streams from agricultural runoff (Taguchi, 1998). Water treatment plants incorporating a chlorination process (e.g., sodium hypochlorite) will produce NDMA from these precursors (Jobb *et al.*, 1993; Graham *et al.*, 1996). Ultraviolet treatment can decompose NDMA to DMA (OME 1994a). However, it is also possible to generate/regenerate NDMA from the DMA within distribution systems that have post-chlorination (Taguchi, 1998). Some treated drinking water samples continue to generate NDMA upon storage, even in the refrigerator at 4°C, because of the presence of the precursors and residual chlorine. These samples have been considered to be "reactive" and are usually analysed within 3 days (OME, 1994b).

In the Section 16 survey under the *Canadian Environmental Protection Act* (CEPA), only two of the companies reported releases of NDMA to the environment (Environment Canada, 1997b). In 1996, a large chemical plant released 29 g of NDMA in wastewater into the St. Clair River. This amount is expected to decrease, as the company installed a wastewater treatment plant in early 1998. A second large chemical plant released 4 g of NDMA into the Canagagigue Creek in 1997. In 1994, this same company released 15 g of NDMA from its kiln stack. The remaining companies reported releasing NDMA in their effluent discharged directly into the local sewage treatment plant at loadings from non-quantifiable to 3000 g.

In a voluntary survey on substances on the Second Priority Substances List (PSL2) sent to Canadian companies, three reported releasing NDMA during the manufacturing process in 1993 (Environment Canada, 1996b). No information on loadings or concentrations, however, was provided by the companies. Under the voluntary Accelerated Reduction/Elimination of Toxics (ARET) program, stakeholders have committed to reducing total emissions of NDMA to all media from 6000 g in 1993 to 87 g by the year 2000 (ARET Secretariat, 1998).

NDMA may be released into the environment as a result of use of certain pesticides contaminated with this compound (Pancholy, 1978). NDMA is present in various technical and commercial pesticides used in agriculture, hospitals and homes as the result of its formation during the manufacturing process and during storage. The following active ingredients in pesticides may contain NDMA as a microcontaminant: bromacil DMA formulation, benazolin DMA formulation (no registered pest control products; discontinued since December 31, 1995), 2,4-D DMA formulation, dicamba DMA formulation, MCPA DMA formulation and mecoprop DMA formulation (Ballantine, 1997; Smith, 1999). Issues related to pesticide contamination are regulated under the *Pest Control Products Act* and Regulations.

Since 1990, the Pest Management Regulatory Agency laboratories, as part of the microcontaminant program, have tested over 100 samples of formulated products (DMA salt of phenoxy acid herbicides) potentially contaminated by NDMA. NDMA was detected in 49% of the samples, with an average concentration of 0.44 µg/g. Only six samples contained NDMA above the Pest Management Regulatory Agency non-regulatory review standard (maximum tolerance) of 1.0 µg/g, with a range from 1.02 to 2.32 µg/g; NDMA

concentrations in pesticides have decreased over time, and this review standard is rarely exceeded (Moore, 1999). In 1994, approximately 1 million kilograms of DMA-formulated phenoxy acid herbicides for commercial use were applied to the terrestrial environment in Canada (Moore, 1999). Based on the average concentration of NDMA mentioned above and percent estimate of detection, it was calculated that approximately 200 g of NDMA may have been released into the environment through the use of these herbicides.

2.3 Exposure characterization

2.3.1 Environmental fate

2.3.1.1 Air

NDMA has a low vapour pressure (1080 Pa at 25°C), and, if emitted to or formed in air, it is not likely to adsorb to airborne particulate matter and is expected to exist almost entirely in the vapour phase. In daylight, it degrades rapidly by direct photolysis to form dimethylnitramine. The photolytic half-life of NDMA vapour exposed to sunlight has been found to range between 0.5 and 1.0 hour (Hanst *et al.*, 1977). Half-lives for the reaction with hydroxyl radicals range from 25.4 to 254 hours in air (Atkinson, 1985). DMER and AEL (1996) selected a mean half-life for NDMA in air of 5 hours in order to calculate environmental partitioning (see Section 2.3.1.6). The short half-lives for NDMA in air suggest that it is not persistent in this compartment.

2.3.1.2 Water

Since NDMA is miscible in water and has a low vapour pressure and a low octanol/water partition coefficient (log K_{ow} of –0.57), it is not likely to bioaccumulate, adsorb to particulates or volatilize to any significant extent (Thomas, 1982; ATSDR, 1989; OME, 1991). Oxidation, hydrolysis, biotransformation and biodegradation are not significant factors affecting the fate of NDMA in lake water (Tate and Alexander, 1975).

Photodegradation is the main process for removing NDMA from the aquatic environment. The efficiency of removal of NDMA depends on the characteristics of the particular water environment. Typically, photodegradation of NDMA is much slower in waters with high concentrations of organic substances and suspended solids than in clear water bodies. The rate of degradation through photolysis may be significantly decreased in the presence of interferences with light transmission, such as ice cover on receiving water bodies (CRA, 1994; McBean, 1999). This observation is supported in the groundwater compartment, where, in the absence of light, NDMA has the potential to persist (OME, 1991).

DMER and AEL (1996) selected a mean half-life of 17 hours for NDMA in surface water at 25°C for use in environmental partitioning (Section 2.3.1.6). Howard *et al.* (1991) reports a half-life range for NDMA in groundwater of 1008–8640 hours, based on estimated unacclimated aqueous aerobic biodegradation.

2.3.1.3 Sediment

DMER and AEL (1996) selected a mean half-life of 5500 hours for NDMA in sediment at 25°C for use in environmental partitioning (Section 2.3.1.6). Factors that slow degradation include anoxic conditions and lack of illumination, the former by preventing the generation of oxidants and the latter by preventing photolysis and the generation of oxidants by photolytic processes.

2.3.1.4 Soil

On soil surfaces, photolysis and volatilization rapidly remove NDMA. Oliver (1979) reported that 30–80% of an unreported concentration of NDMA volatilized from the soil within the first few hours of application to the soil surface. Once incorporated into subsurface soil, however, NDMA will be highly mobile, with the potential to migrate into groundwater supplies. Subsurface biodegradation is slightly slower under anaerobic

than under aerobic conditions (ATSDR, 1989). Soil type only slightly affects biodegradation of NDMA. Aeration of soil improved biodegradation compared with waterlogged soil. Pre-exposure of bacteria to NDMA increased biodegradation in soil (Mallik and Tesfai, 1981). DMER and AEL (1996) selected a mean half-life of 1700 hours for NDMA in soil at 25°C for use in environmental partitioning (Section 2.3.1.6).

2.3.1.5 Biota

Although NDMA is not present in plants under natural conditions, it can be taken up from the growth medium. Lettuce and spinach plants absorb NDMA from sand, soil and water after exposure for 2 days to concentrations ranging from 10 to 100 mg NDMA/kg wet weight, with 3.25% and 0.38% being taken up from the growth medium by lettuce and spinach plants, respectively (Dean-Raymond and Alexander, 1976).

A bioconcentration factor of 0.2 has been estimated for NDMA (Bysshe, 1982). However, OME (1998a) observed that a conventional estimate of a bioconcentration factor (correlation with K_{ow}) is not applicable, because biota generally can biotransform NDMA.

2.3.1.6 Environmental partitioning

Fugacity modelling was carried out to provide an overview of key reaction, intercompartment and advection (movement out of a system) pathways for NDMA and its overall distribution in the environment. A steady-state, non-equilibrium model (Level III fugacity model) was run using the methods developed by Mackay (1991) and Mackay and Paterson (1991). Assumptions, input parameters and results are presented in DMER and AEL (1996) and summarized here: molecular weight, 74.08 g/mol; water solubility, miscible; vapour pressure, 1080 Pa; log K_{ow}, –0.57; Henry's law constant, 3.34 Pa·m³/mol; half-life in air, 5 hours; half-life in water, 17 hours; half-life in soil, 1700 hours; half-life in sediment, 5500 hours. Modelling was based on an assumed default emission rate of 1000 kg/hour into a region of 100 000 km², which includes a surface water area (20 m deep) of 10 000 km². The height of the atmosphere was assumed to be 1000 m. Sediments and soils were assumed to have an organic carbon content of 4% and 2% and a depth of 1 cm and 10 cm, respectively. The estimated percent distribution predicted by this model is not affected by the assumed emission rate.

Fugacity modelling indicates that NDMA behaves differently depending on the medium to which it is released. Generally, when NDMA is continuously released into a medium, most of it will be found in that medium at steady state. For example, if NDMA is discharged into water, almost all of it will be found in the aqueous phase, with very small amounts in air and soil. Almost all of the NDMA is removed by reaction in water. Similarly, most NDMA released to air will exist in the atmosphere, with very small amounts in soil and water. Finally, when NDMA is discharged continuously to soil, almost all of the substance is transported to surface water, and about a third goes into the atmosphere. However, since NDMA is much more persistent in soil than in water or air at steady state, almost all of the NDMA is found in soil, with very little found in surface water, and even less found in the atmosphere (DMER and AEL, 1996).

In summary, the Level III fugacity model predicts that if NDMA is emitted into water or air, it will be found in, and react in, the medium of discharge. Emission of NDMA into water or air will tend to result in localized contamination of short duration. If emitted to soil, NDMA moves to the water or air compartments, where it undergoes reaction, or it reacts slowly in the soil. Because rates of volatilization, absorption, runoff and reaction in soil are relatively slow compared with reaction in air and water, the persistence of NDMA emitted to soil is longer, and there is potential for NDMA to move into the groundwater compartment (DMER and AEL, 1996).

2.3.2 *Environmental concentrations*

2.3.2.1 Ambient air

There is little information concerning the presence or concentrations of NDMA in ambient (i.e., outdoor) air in Canada or elsewhere. Limited Canadian data are restricted to the province of Ontario, where short-term measurements have been taken in the immediate vicinity of potential point sources of discharge to the atmosphere, for comparison with background measurements from other urban locations. No data on airborne concentrations at rural locations were identified.

At industrial and urban locations in Ontario in 1990, based on seven samples taken in five cities, concentrations of NDMA were all below the detection limit (detection limits ranged from 0.0034 to 0.0046 μg/m^3) (OME, 1990). Based on 51 30-minute samples taken in the city of Windsor, Ontario, in August 1991, concentrations of NDMA were all below the detection limits, which ranged from 0.0014 to 0.017 μg/m^3 (OME, 1994b).

In surveys during 1990 of a chemical production facility in Elmira, Ontario, concentrations of NDMA ranged from not detected (detection limits ranged from 0.0029 to 0.0048 μg/m^3) to 0.230 μg/m^3, based on 41 samples; concentrations in 20 of the 41 samples were at or above the detection limit (OME, 1990). The highest concentrations were measured within the perimeter of the production facility, while the maximum concentration measured beyond this perimeter was 0.079 μg/m^3. Concentrations in 22 of 40 samples taken in the vicinity of an industrial site in Kitchener, Ontario, in the summer of 1992 ranged from the detection limit (0.0017–0.0042 μg/m^3) to 0.14 μg/m^3 (OME, 1992a). In 1994, at a chemical plant near Elmira, Ontario, two air samples taken from the top of the kiln stack contained NDMA at the detection limit (0.17 μg/m^3) and at 0.35 μg/m^3 (Environment Canada, 1997b).

2.3.2.2 Indoor air

No data were identified concerning the presence or concentrations of NDMA in indoor air from residential or public locations in Canada. Available data indicate that levels of NDMA were elevated in indoor air contaminated with environmental tobacco smoke (ETS) in the United States (Brunnemann and Hoffmann, 1978) and Austria (Stehlik *et al.*, 1982; Klus *et al.*, 1992). The maximum concentration of NDMA in ETS-contaminated indoor air was 0.24 μg/m^3, whereas NDMA was not detected (i.e., <0.003 μg/m^3) when the indoor air of a residence of a non-smoker was sampled in the same manner (Brunnemann and Hoffmann, 1978). Concentrations of NDMA in ETS-contaminated indoor air in these countries were generally between 0.01 and 0.1 μg/m^3 (Health Canada, 1999).

2.3.2.3 Water

Releases of NDMA to water in Canada have been measured primarily in Ontario. In 1996, a chemical plant released wastewater containing NDMA into the St. Clair River at a concentration of 0.266 μg/L (Environment Canada, 1997b). In April 1997, concentrations of NDMA at the point of release to surface water ranged from 0.096 to 0.224 μg/L for this company. These concentrations are expected to decrease, as the company installed a wastewater treatment plant in early 1998. A second large chemical plant released 0.04 μg NDMA/L to Canagagigue Creek in 1997 (Environment Canada, 1997b). In an 8-week survey in spring 1992, average concentrations in surface water of the Canagagigue Creek ranged from not detectable (<0.05 μg/L) to 0.36 μg/L in 65 samples (16 above detection limit) (OME, 1992b). In 1989, NDMA concentrations above 1 μg/L in industrial discharges were detected in effluent from a chemical plant producing rubber chemicals, a rubber plant producing hoses and belts, and a pulp fibre de-inking and recovery operation (OME, 1991).

In 1994, a sanitary discharge from a re-refinery in Ontario resulted in concentrations up to 65 µg NDMA/L (OME, 1994c). In a survey of sewage treatment plant effluent in Ontario in 1990, NDMA was detected in 27 of 39 samples, with the maximum concentration being 0.22 µg/L (unpublished 1990 data, as cited in OME, 1991). Although NDMA may be formed during sewage treatment, the typical background concentrations associated with sewage treatment plant operations have not been characterized (OME, 1991). In 1996, four companies reporting under Section 16 of CEPA released NDMA in effluent into the local sewage treatment plant (Environment Canada, 1997b).

Under the Ontario Drinking Water Surveillance Program, 390 samples of raw surface water from 101 water treatment plants were sampled for NDMA. Data collected from 1990 to July 1998 indicated that 37 plants had detectable concentrations (>0.001 µg/L) in the raw water. The average concentration in raw water was 1.27×10^{-3} µg/L. The highest concentration of NDMA in raw water was 0.008 µg/L from two water treatment plants in 1996 (OMEE, 1996; OME, 1998b).

In 1997–1998, a joint Environment Canada/provincial survey of monitoring by municipal drinking water treatment facilities and distribution systems was conducted. Only one municipality in Ontario (the Regional Municipality of Ottawa-Carleton) reported sampling for NDMA in its raw and treated water in 1995 and 1996. In 1995, NDMA was not detected (<0.001 µg/L) in four samples of raw water and was detected in one of six samples of treated water at a concentration of 0.003 µg/L. In 1996, NDMA was not detected (<0.15 µg/L) in two and four samples of raw and treated water, respectively (Environment Canada, 1998).

In 1990, under the Ontario Drinking Water Surveillance Program, concentrations of NDMA in 24 groundwater samples taken from various locations in Ontario were below detection limits (detection limits ranged from 0.001 to 0.010 µg/L). Concentrations of NDMA in the municipal aquifer in Elmira ranged from 1.3 to 2.9 µg/L, attributed to contamination from a nearby chemical facility (unpublished 1990 data, as cited in OME, 1991). The municipal wells using this aquifer were closed in 1989 (OME, 1989). In 1994 and 1995, concentrations of up to 0.005 µg NDMA/L (detection limit 0.001 µg/L) in raw surface water and groundwater supplies in rural areas in southern Ontario were reported (OME, 1991).

There were 313 samples of treated water analysed from 100 locations within Ontario under the Drinking Water Surveillance Program between 1994 and 1996. NDMA was detected (i.e., at greater than 0.001 µg/L) in at least one sample at 40 of these 100 sites. The proportion of samples in which NDMA was detected was 45% (i.e., 140 of 313 samples). The censored mean concentration was 0.0027 µg/L when a concentration equivalent to one-half the limit of detection (i.e., 1/2 × 0.001 µg/L = 0.0005 µg/L) was assumed for the 173 samples in which NDMA was not detected.

The highest concentrations were measured in samples from drinking water plants using a specific pre-blended polyamine/alum water treatment coagulant (OMEE, 1996). These included a concentration of 0.04 µg/L at the water treatment plant in Huntsville, Ontario. NDMA was detected in all (i.e., at greater than 0.001 µg/L) 20 samples collected from four water treatment plants using the specific coagulant. The mean concentration of NDMA in these 20 samples was 0.012 µg/L, whereas the (censored) mean concentration in the remaining 293 samples for the locations where the specific coagulant was not used was 0.002 µg/L (irrespective of whether a value of zero, one-half the limit of detection or the limit of detection was assumed for the concentration of NDMA in samples in which it was not detected).

Treatment studies on groundwater at a chemical plant in southern Ontario indicated that activated sludge can accumulate NDMA, particularly when nitrification and denitrification are applied to increase the sludge age. Concentrations of NDMA sampled in activated sludge ranged from 5 to 10 mg/L (Kochany, 1999; McBean, 1999). In the United States, NDMA has been reported to be a common constituent of sewage sludge. Concentrations ranging from 0.6 to 45 µg/g were found in the dried sludge from 14 of 15 cities (Mumma *et al.*, 1984).

2.3.2.4 Sediment and soil

No data on concentrations of NDMA in sediments or soils in Canada were identified.

2.3.2.5 Human tissues

NDMA has been quantitated in a variety of tissues and biological fluids. In a study conducted in Quebec, Cooper *et al.* (1987) detected NDMA in the liver, kidneys, brain and pancreas from four (non-occupationally exposed) individuals at postmortem; concentrations ranged from approximately 0.12 to 0.9 ng/g tissue. In studies conducted outside of Canada, reported levels of NDMA in the blood or plasma of non-occupationally exposed individuals have ranged from approximately 0.03 to 1.5 ng/mL (Fine *et al.*, 1977; Lakritz *et al.*, 1980; Yamamoto *et al.*, 1980; Garland *et al.*, 1982; Gough *et al.*, 1983; Dunn *et al.*, 1986). In other studies, concentrations of NDMA in breast milk ranged from 0.1 to 1.8 ng/g (Lakritz and Pensabene, 1984; Mizuishi *et al.*, 1987; Uibu *et al.*, 1996). NDMA has been detected in the urine of individuals having no clearly defined exposure to this nitrosamine; reported concentrations from studies conducted in Canada (Kakizoe *et al.*, 1979) and elsewhere (Lakritz *et al.*, 1982; Webb *et al.*, 1983) have ranged from 0.02 to 0.2 ng/mL.

2.3.2.6 Food

NDMA can be formed during food processing, preservation and/or preparation from precursor compounds already present in, or added to, the specific food items. The foodstuffs that have been most commonly contaminated with NDMA can be classified into several broad groups:

1) foods preserved by the addition of nitrate and/or nitrite, such as cured meat products (in particular, bacon) and cheeses (since these methods of preservation introduce nitrosating species into the food);

2) foods preserved by smoking, such as fish and meat products (since oxides of nitrogen in the smoke act as nitrosating agents);

3) foods dried by combustion gases, such as malt, low-fat dried milk products and spices (since combustion gases can contain oxides of nitrogen); and

4) pickled and salt-preserved foods, particularly pickled vegetables (since microbial reduction of nitrate to nitrite occurs).

Since 1975, efforts have been made to reduce the potential for exposure to NDMA in foodstuffs in Canada through continued reduction of allowable nitrite levels during preservation and suspension of the use of nitrate for certain food groups made through changes to the Food and Drugs Regulations. In regulations amended in 1975, permissible levels of nitrite in cured meat products were lowered and the use of nitrate was eliminated, except for a few classes of products (including "slow-cured" meats) (Lawrence, 1999). For example, the permitted level of use of nitrite in bacon, in which the potential for formation of nitrosamines is greatest, was lowered from 200 to 150 mg/kg. A further amendment in 1985 lowered the permitted maximum level of use of potassium nitrite and sodium nitrite from 150 to 120 mg/kg in cured side bacon. The use of nitrate

in seafood preservation was suspended in 1965, shortly after inception of the Food Additive Tables in 1964 (Salminen, 1999).

Data concerning the concentrations of NDMA in Canadian food items from each of the groups in which there is potential for exposure are limited and largely predate the introduction of controls outlined above. Concentrations of NDMA in 121 samples of various meat products in Canada ranged from less than 0.1 µg/kg (the limit of detection) to a maximum of 17.2 µg/kg in a sample of bacon (Sen *et al.*, 1979, 1980b). Concentrations of NDMA in 63 samples of various fish and seafood products in Canada ranged from less than 0.1 µg/kg (the limit of detection) to a maximum of 4.2 µg/kg in a sample of salted/dried fish (Sen *et al.*, 1985). Concentrations of NDMA in 62 samples of cheese (31 of Canadian origin and 31 imported) purchased in Canada ranged from less than 1 µg/kg (the limit of detection) to a maximum of 68 µg/kg in a sample of wine cheese (Sen *et al.*, 1978).

NDMA was generally not detected in samples of milk products, except for skim milk powder, where it was present in all 11 samples, at a maximum concentration of 0.7 µg/kg (Sen and Seaman, 1981b). In other countries, the presence of NDMA in non-fat dried milk powders has been attributed to the use of natural gas for direct fired heating (Kelly *et al.*, 1989; Scanlan *et al.*, 1994). In Canada, in other foods dried directly, NDMA was detected in 1 of 10 samples of instant coffee at a concentration of 0.3 µg/kg and in 2 of 20 samples of dried soup with a maximum concentration of 0.25 µg/kg (Sen and Seaman, 1981b).

NDMA was not detected (at limits of detection ranging from 0.1 to 0.5 µg/kg) in 25 samples of baby food, including formula, cereal and mixed food containing meat, analysed from 1979 to 1981 (Sen *et al.*, 1979, 1980b; Sen and Seaman, 1981b). In a survey of other food products in 1979, NDMA was not detected in apple juice or drink, ketchup and other sauces, Ovaltine, margarine, butter, lard or (fresh and canned) mushrooms (Sen *et al.*, 1980b). The limit of detection was 0.1 µg/L or 0.1 µg/kg. NDMA was detected at a trace level (<0.2 µg/kg) in 1 of 11 samples of pizza and pizza toppings (Sen *et al.*, 1980b).

Among the cured meat products analysed, bacon was unique, in that it was generally free of nitrosamines in the raw stage. Nitrosamines were formed in bacon only during high-heat frying (Sen *et al.*, 1979). Various factors control the formation of NDMA in fried bacon, including the initial and residual levels of nitrite, processing conditions, the diet of the pigs, the lean to adipose tissue ratio, the presence of inhibitors, frying temperatures and cooking methods (Sen, 1986). The cooked-out fat contains higher (approximately twice as high) levels of nitrosamines than the cooked lean bacon, and steam-volatile nitrosamines such as NDMA are volatilized in the fumes produced during frying (Sen, 1986).

Concentrations of NDMA in bacon currently consumed in Canada are unlikely to be as high as the maximum of 17.2 µg/kg reported previously (Sen *et al.*, 1979, 1980b), as a result of the controls on the use of nitrate and nitrite in cured meat products introduced in Amendments to the Canadian Food and Drugs Regulations in 1975. However, quantitative data are not available to support this conclusion.

There is consensus among the literature surveyed that concentrations of NDMA in foods from developed countries were an order of magnitude lower in the late 1980s and early 1990s than in the 1970s (Tricker *et al.*, 1991a; Cornée *et al.*, 1992; Sen *et al.*, 1996). The reduction in the concentrations of preformed NDMA in foods is attributed to improvements in food cooking and preservation techniques. However, no data are available with which to determine whether the concentrations of preformed NDMA in foods in Canada or

elsewhere have continued to decline throughout the 1990s or remain at the levels measured in the late 1980s and early 1990s.

Most malt beverages, including beer and most brands of whiskey, regardless of origin, contain NDMA (ATSDR, 1989). The presence of NDMA in beer was first reported in 1977 (Sen *et al.*, 1980a; OME, 1991). Malt was found to be the main source of NDMA contamination in beer, and NDMA was shown to be formed during direct drying of malt using hot flue gases — a practice that was common prior to 1980 (Spiegelhalder *et al.*, 1980). Improved malt drying techniques (direct to indirect in 1981) have now significantly reduced the levels of NDMA in malt and beer (OME, 1991; Sen *et al.*, 1996). It is currently believed that NDMA is only a minor component of the total *N*-nitroso compounds in beer and that the major contribution is made by as yet unidentified non-volatile *N*-nitroso compounds (Massey *et al.*, 1990; U.K. MAFF, 1992). Among samples of beer produced in Canada, a maximum concentration of 4.9 µg/L was reported in a beer from Ontario in 1978, while in more recent samples (i.e., 1988–1989), the maximum concentration was 0.59 µg/L. Among imported beers purchased in Canada, a maximum concentration of 9.2 µg/L was reported in a beer sampled in 1991–1992, while in more recent samples (i.e., October–December 1994), the maximum concentration was 3.2 µg/L.

NDMA may also be endogenously produced *in vivo* from precursor compounds contained in the food ingested (e.g., DMA in meats and fish and nitrate/nitrite in vegetables) and/or already present in the human body (e.g., nitrate, nitrite). Urinary excretion of NDMA was significantly increased in human volunteers after intake of nitrate in drinking water in combination with a fish meal (Vermeer *et al.*, 1998). Fish was selected, as it contains high amounts of amines, including DMA (Sen *et al.*, 1985).

Available data are inadequate to serve as a basis for determining the quantities of endogeneous NDMA formed or their relative contribution to exposure via ingestion compared with NDMA's exogenous presence in food (Cornée *et al.*, 1992).

2.3.2.7 Consumer products

Exposure can result from the use of consumer products that contain NDMA, such as cosmetics and personal care products, products containing rubber and tobacco products.

NDMA has been detected in a variety of personal care and cosmetic products (e.g., shampoos, hair conditioners and toners, bath and shower gels, creams and oils, face tonics, cleansers), likely due to the reaction of nitrosating agents such as nitrite and/or nitrogen oxides, which occur frequently therein (Spiegelhalder and Preussmann, 1984), with amine-containing compounds, which are used extensively in ingredients of personal care products. Examples include surfactants, detergents, foam boosters, protein additives and colouring agents (ECETOC, 1990). Ingredients that might in some circumstances give rise specifically to NDMA include quaternary ammonium compounds, betaines and amine oxides (ECETOC, 1991). Nitrosation in cosmetic matrices is often slow, but cosmetic products may remain on store shelves and in consumers' cabinets for extended periods of time, during which nitrosamines can continue to form in the products (Havery and Chou, 1994).

Fifty (or 34.5%) of 145 products surveyed in Germany in 1984 contained NDMA, at a maximum concentration of 24 µg/kg in one shampoo (Spiegelhalder and Preussmann, 1984). However, while data on concentrations of NDMA in Canadian cosmetic products were not identified, current levels of NDMA in Canadian products are likely much lower than these levels. Indeed, Health Canada recommends for cosmetic notifications that manufacturers ensure that their raw materials are not contaminated with nitrosamines, and that their formulations do not include combinations of nitrosating agents and

amines/amides. Manufacturers who submit cosmetic notifications for formulations that include combinations of such precursor substances are requested to provide evidence that the level of nitrosamines present in the product or formed over a period equivalent to the shelf life of the product does not exceed 10 µg/kg. Failing this, manufacturers are required to reformulate the products to remove either the amines/amides or the nitrosating agents (Green, 1995).

Rubber-containing products that come into contact with human skin are another potential source of exposure to NDMA, since dialkylamines used by rubber manufacturers as accelerators and stabilizers during rubber vulcanization can react with nitrosating agents during processing to form nitrosamines (Biaudet *et al.*, 1997). NDMA has been detected in a diverse selection of workplace, consumer and medical products containing rubber (Health Canada, 1999). The maximum concentration of NDMA detected (i.e., 329 mg/kg) was in latex disposable protective gloves in the United States. However, only a small proportion of the total nitrosamines in the gloves would be expected to be leached out and dermally absorbed (Fiddler *et al.*, 1985). *N*-Nitrosamines have been detected in baby bottle rubber nipples and pacifiers in Canada. The maximum concentrations of NDMA reported in the published literature were 25 mg/kg in baby bottle rubber nipples and 8.6 mg/kg in rubber pacifiers (Sen *et al.*, 1984).

Currently, in Canada, however, under the *Hazardous Products Act* and Regulations, infant feeding bottle nipples and pacifiers may not contain more than 10 mg total volatile *N*-nitrosamines/kg, as determined by dichloromethane extraction (Health Canada, 1999). The determination of nitrosamines is conducted according to a cyclical enforcement policy, which calls for a survey of samples of products representative of those available in the Canadian market at least every 6 years. In surveys conducted in 1995 and 1998, NDMA was not detected (detection limit 1 mg/kg); the next survey is scheduled for fiscal year 2001–2002 (Wright, 1999).

The nitrosation of natural constituents of tobacco during curing and fermentation results in the formation of three major classes of *N*-nitroso compounds in tobacco and tobacco products — volatile, non-volatile and tobacco-specific *N*-nitrosamines (Hoffmann *et al.*, 1984; Tricker *et al.*, 1991b). In addition, the combustion of cigarette tobacco results in the pyrolytic formation of volatile *N*-nitrosamines, including NDMA (Tricker and Preussmann, 1992). The yields of these volatile *N*-nitrosamines in cigarette smoke from combustion of tobacco depend on many chemical and physical parameters, including the amounts of organic nitrogen and nitrate present (Hoffmann *et al.*, 1987). Furthermore, nicotine serves as a specific precursor for formation of NDMA (Hoffmann *et al.*, 1987).

The NDMA content of cigarette and oral tobacco and the amounts of NDMA in mainstream smoke, sidestream smoke and ETS have been assessed in several studies (Health Canada, 1999). The levels of preformed volatile *N*-nitrosamines in the cigarette tobacco are considerably lower than the corresponding levels in the mainstream smoke (Tricker *et al.*, 1991b), and the levels of NDMA in sidestream smoke are generally 1 or 2 orders of magnitude greater than in the mainstream smoke from the same cigarette (Health Canada, 1999).

In other studies, emissions of NDMA and other *N*-nitrosamines in ETS rather than in sidestream smoke have been determined. The determination of emission factors (e.g., ng/cigarette) of nitrosamines (and other smoke constituents) in ETS requires measurements in environmental chambers. The measured concentrations and calculated emission factors are highly sensitive to operating conditions in these chambers (e.g., chamber volume, air exchange rate); however, the environmental chamber is thought to more closely simulate real smoking environments.

The average ETS emission factor for NDMA for six U.S. commercial cigarette brands was 570 ± 120 ng/cigarette (CARB, 1994; Mahanama and Daisey, 1996). These data have been extrapolated to estimate the concentration of NDMA in indoor air spaces of defined volume and air exchange rates. The predicted concentrations of NDMA in indoor air ranged from 0.002 to 0.005 mg/m^3 (Mahanama and Daisey, 1996). Predicted concentrations based on data from other studies ranged from 0.011 to 0.037 mg/m^3 (Mahanama and Daisey, 1996). These modelled concentrations are similar to the measured concentrations of NDMA in indoor air contaminated with ETS, summarized in Section 2.3.2.2.

2.4 Effects characterization

2.4.1 Ecotoxicology

The effects of NDMA resulting from acute and chronic exposure have been extensively studied in a variety of species of aquatic plants and animals. A brief summary of effects is presented below, with emphasis on the most sensitive endpoints for aquatic organisms. Studies summarized below were critically reviewed in the following reports: OME (1991, 1998a) and ATSDR (1989).

2.4.1.1 Aquatic organisms

Green algae (*Selenastrum capricornutum*) and blue-green algae (*Anabaena flos-aqua*) were exposed to NDMA over a 13-day period in static systems. The test was conducted to determine effects on algal growth rate, cell number, maximum standing crop and dry weight. The 13-day EC_{50}s for growth were 4 mg/L and 5.1 mg/L for the green and blue-green algae, respectively (Draper and Brewer, 1979).

Draper and Brewer (1979) reported a 96-hour LC_{50} of 940 mg/L for fathead minnow (*Pimephales promelas*) and a 96-hour LC_{50} of 1365 mg/L for flatworms (*Dugesia dorotocephala*). For scud (*Gammarus limnaeus*), 96-hour LC_{50} values ranged from 280 to 445 mg/L (Draper and Fisher, 1980). Both studies were conducted in static renewal systems.

The LC_{50} values for a saltwater fish, the common mummichog (*Fundulus heteroclitus*), in a static non-renewal system were 8300 mg/L at 24 hours, 5500 mg/L at 48 hours, 4700 mg/L at 72 hours, 3300 mg/L at 96 hours and 2700 mg/L at 120 hours (Ferraro *et al.*, 1977).

Grieco *et al.* (1978) reported a dose-related increase in hepatocellular carcinomas in a study in which rainbow trout (*Oncorhynchus mykiss*) received 3, 200, 400 or 800 mg NDMA/kg in the diet over 52 weeks. Tumours did not form in trout receiving 3 mg/kg, although body weight was reduced. OME (1998a) observed that growth reduction in rainbow trout was a more sensitive response than tumour induction.

Frogs (*Rana temporaria*) were exposed to 5 mg NDMA/L in water for 63 days and 203 days. In both studies, the frogs developed hepatocellular carcinomas as well as adenomas and tumours of the hematopoietic system. Approximately 44% of the frogs exposed for 203 days developed tumours (Khudoley, 1977). In another species of frog (*Xenopus borealis*) exposed for 52 weeks to 400 mg NDMA/L in aquarium water, 54% of the test animals developed liver and kidney tumours (Khudoley and Picard, 1980). The authors believed that amphibians were more sensitive (shorter latency period and higher tumour incidence) than fish to the carcinogenic effects of the nitrosamine.

2.4.2 Abiotic atmospheric effects

Worst-case calculations were made to determine if NDMA has the potential to contribute to the depletion of stratospheric ozone, ground-level ozone formation or climate change (Bunce, 1996).

The Ozone Depletion Potential (ODP) is 0, as NDMA is not a halogenated compound.

The Photochemical Ozone Creation Potential (POCP) was estimated to be 11.3 (relative to the value of an equal mass of the reference compound ethene, which has a POCP of 100), based on the following formula:

$$POCP = (k_{NDMA}/k_{ethene}) \times (M_{ethene}/M_{NDMA}) \times 100$$

where:

- k_{NDMA} is the rate constant for the reaction of NDMA with OH radicals (2.53×10^{-12} cm³/mol per second),
- k_{ethene} is the rate constant for the reaction of ethene with OH radicals (8.5×10^{-12} cm³/mol per second),
- M_{ethene} is the molecular weight of ethene (28 g/mol), and
- M_{NDMA} is the molecular weight of NDMA (74.08 g/mol).

The Global Warming Potential (GWP) was calculated to be 5.0×10^{-4} (relative to the reference compound CFC-11, which has a GWP of 1), based on the following formula:

$$GWP = (t_{NDMA}/t_{CFC\text{-}11}) \times (M_{CFC\text{-}11}/M_{NDMA}) \times (S_{NDMA}/S_{CFC\text{-}11})$$

where:

- t_{NDMA} is the lifetime of NDMA (0.016 years),
- $t_{CFC\text{-}11}$ is the lifetime of CFC-11 (60 years),
- $M_{CFC\text{-}11}$ is the molecular weight of CFC-11 (137.5 g/mol),
- M_{NDMA} is the molecular weight of NDMA (74.08 g/mol),
- S_{NDMA} is the infrared absorption strength of NDMA (2389/cm² per atmosphere, default), and
- $S_{CFC\text{-}11}$ is the infrared absorption strength of CFC-11 (2389/cm² per atmosphere).

These figures suggest that the potential contribution of NDMA to stratospheric ozone depletion, to ground-level ozone formation and to climate change is negligible. Also, these calculations do not consider the short photolytic half-life of NDMA vapour in sunlight (i.e., 0.5–1.0 hour; Hanst *et al.*, 1977), resulting in a seriously overestimated GWP and POCP. Finally, the environmental impact of NDMA emissions to the atmosphere will be much smaller than that of the ozone-forming reference compound ethene, because much smaller quantities of NDMA are emitted (Bunce, 1996).

2.4.3 *Experimental animals and* in vitro

2.4.3.1 Acute toxicity

NDMA is highly acutely toxic after oral administration to rats, with LD_{50}s ranging from 23 to 40 mg/kg-bw. It is also highly acutely toxic via inhalation; 4-hour LC_{50}s are 78 ppm (240 mg/m³) for rats and 57 ppm (176 mg/m³) for mice. One day after three dogs were exposed (via inhalation) to 16 ppm (49 mg/m³) NDMA for 4 hours, one had died, and the others were moribund (ATSDR, 1989). In all three species, acute inhalation exposure produced hemorrhagic necrosis in the liver; an increased blood clotting time was reported for the NDMA-exposed dogs (ATSDR, 1989). In other laboratory species, acute exposure to NDMA produced effects in the liver (hepatotoxicity), kidney (tumours) and testes (necrosis of the seminiferous epithelium) (Magee and Barnes, 1962; Schmidt and Murphy, 1966; Hard and Butler, 1970a,b; McLean and Magee, 1970; OME, 1991).

2.4.3.2 Short-term and subchronic toxicity

Hepatic effects (i.e., hepatocyte vacuolization, portal venopathy and necrosis/hemorrhage), often associated with reduced survival, have been observed in a number of mammalian species exposed under various conditions (e.g., in rats receiving 1, 3.8 or 5 mg NDMA/kg-bw per day for 30, 7–28 or 5–11 days, respectively; in mice receiving 5 mg/kg-bw per day for 7–28 days; in hamsters receiving 4 mg/kg-bw per day for 1–28 days; in guinea pigs, cats and monkeys receiving 1 or 5 mg/kg-bw per day for 30 or 5–11 days,

respectively; in dogs receiving 2.5 mg/kg-bw per day, 2 days per week, for 3 weeks; and in mink receiving 0.32 mg/kg-bw per day for 23–34 days) (ATSDR, 1989).

In addition to effects in the liver, "congestion" in a variety of organs (i.e., kidneys, lung, spleen and myocardium) has been reported following gross examination of rats receiving 3.8 mg NDMA/kg-bw per day in the diet for 1–12 weeks; the results of histopathological examination were not reported (Khanna and Puri, 1966). Gastrointestinal hemorrhage has been observed in rats receiving dietary doses of 10 mg NDMA/kg-bw per day for 34–37 days (Barnes and Magee, 1954) and in mink receiving 0.3 or 0.6 mg NDMA/kg-bw per day in the diet for 23–34 days (Carter *et al.*, 1969). Effects in the kidneys (including glomerulus dilatation and slight thickening of the Bowman's capsule) were observed in mink receiving 0.2 mg NDMA/kg-bw per day from the diet (period not specified) (Martino *et al.*, 1988).

2.4.3.3 Carcinogenicity

Although most studies were conducted early and would be considered limited by today's standards, clear evidence of carcinogenicity has been observed in a number of studies in which rodents (i.e., rats, mice, hamsters) were exposed to NDMA orally, via inhalation or by intratracheal instillation. NDMA increased the incidence of liver and Leydig cell tumours in rats ingesting this nitrosamine from drinking water or the diet (Terao *et al.*, 1978; Arai *et al.*, 1979; Ito *et al.*, 1982; Lijinsky and Reuber, 1984); increased tumour incidences were noted at NDMA concentrations of about 5 mg/L in drinking water and 10 mg/kg in the diet. Increased incidences of nasal, hepatic, pulmonary and renal tumours were observed in rats exposed to NDMA via inhalation (Moiseev and Benemanskii, 1975; Klein *et al.*, 1991); increases in the incidence of hepatic, pulmonary and renal tumours were observed following exposure to NDMA at a concentration of 0.2 mg/m^3 (Moiseev and Benemanskii, 1975). Hepatic, pulmonary and renal carcinogenicity was observed in mice administered NDMA via drinking water (Terracini *et al.*, 1966; Clapp and Toya, 1970; Anderson *et al.*, 1979, 1986, 1992b) or through inhalation (Moiseev and Benemanskii, 1975); increases in tumour incidence were observed at concentrations of NDMA in drinking water ranging from 0.01 to 5 mg/L. Moreover, in some cases (e.g., Terracini *et al.*, 1966), the period of exposure to NDMA was relatively short (i.e., 3 weeks). In mice administered NDMA via drinking water or intragastrically, co-exposure with ethanol increased the pulmonary carcinogenicity of the nitrosamine (Anderson, 1988; Anderson *et al.*, 1992b), an effect attributed to inhibition of the (first-pass) metabolism of NDMA in the liver by the alcohol. NDMA increased the incidence of liver tumours in hamsters exposed intratracheally (Tanaka *et al.*, 1988). The administration of NDMA to pregnant rats (by intraperitoneal injection) or mice (by stomach tube) increased the frequency of hepatic and renal tumours in the offspring (Alexandrov, 1968; Anderson *et al.*, 1989). An increased incidence of renal tumours has also been observed in rats administered either a single oral (Magee and Barnes, 1962) or intraperitoneal (Hard and Butler, 1970a; McLean and Magee, 1970) dose of NDMA (at levels of 30–60 mg/kg-bw).

In a more recently conducted comprehensive carcinogenicity bioassay (designed to provide detailed information on exposure–response) involving lifetime exposure (i.e., animals were exposed continuously until natural death), 15 dose groups of 60 male and 60 female Colworth-Wistar rats were provided with drinking water containing NDMA covering a wide range of concentrations[1] (see Tables 2 and 3) (Brantom, 1983; Peto *et al.*, 1991a,b). The estimated daily intakes of NDMA ranged from 0.001 to 0.697 mg/kg-bw in the males and from 0.002 to 1.224 mg/kg-bw in the females. A

[1] The concentrations of NDMA were 33, 66, 132, 264, 528, 1056, 1584, 2112, 2640, 3168, 4224, 5280, 6336, 8448 and 16 896 µg/L.

control group of 120 males and 120 females received drinking water without NDMA (Brantom, 1983; Peto *et al.*, 1991a,b). Groups of animals were taken for interim sacrifice after 12 and 18 months of study. Dose-related increases in tumour incidence were observed only in the liver in both males and females (see Tables 2 and 3). The increase in tumour incidence was greatest for hepatocellular carcinoma and biliary cystadenoma. For some other sites (i.e., pituitary and thyroid in males, and pituitary, uterus, thymus and mammary tissue in females), the incidence of tumours declined with increasing exposure to NDMA.

Non-neoplastic effects observed in the liver included hyperplastic nodules and the shrinkage of hepatocytes. Peto *et al.* (1991a,b) conducted detailed analyses relating the development of liver tumours in these animals to the period of exposure and dose of NDMA administered. These authors concluded that in rats exposed to low levels of NDMA starting at 6 weeks of age, mortality due to liver cancer would be approximately 7-fold greater in the animals allowed to succumb naturally than in those exposed to the nitrosamine for only 2 years.

TABLE 2 Carcinogenicity study with male rats[1]

Exposure group	NDMA concentration in drinking water (mg/L)	Estimated intake (mg/kg-bw per day)[2]	Animals with hepatic tumours (%)[3]		
			Carcinoma	Hemangio-sarcoma	Biliary cystadenoma
1	0	0	1	1	1
2	0.033	0.001	2	0	4
3	0.066	0.003	2	0	4
4	0.132	0.005	4	2	4
5	0.264	0.011	2	4	4
6	0.528	0.022	6	0	2
7	1.056	0.044	10	2	2
8	1.584	0.065	13	2	8
9	2.112	0.087	10	13	13
10	2.640	0.109	25	13	23
11	3.168	0.131	29	29	27
12	4.224	0.174	33	21	25
13	5.280	0.218	58	6	29
14	6.336	0.261	60	15	40
15	8.448	0.348	77	6	29
16	16.896	0.697	88	6	4

[1] Brantom (1983); Peto *et al.* (1991a,b). Animals were provided, for their entire lives until natural death, drinking water containing the indicated concentrations of NDMA. The animals were sacrificed and necropsied if moribund or exhibiting palpable liver alterations.

[2] Intakes estimated by authors (Peto *et al.*, 1991b).

[3] Proportion of animals with tumours specified at each dose level; n = 192 for unexposed controls (treatment group 1); n = 48 for each dose level (treatment groups 2–16) (Brantom, 1983).

TABLE 3 Carcinogenicity study with female rats[1]

Exposure group	NDMA concentration in drinking water (mg/L)	Estimated intake (mg/kg-bw per day)[2]	Animals with hepatic tumours (%)[3]		
			Carcinoma	Hemangio-sarcoma	Biliary cystadenoma
1	0	0	1	1	2
2	0.033	0.002	0	2	2
3	0.066	0.005	0	0	8
4	0.132	0.010	4	2	0
5	0.264	0.019	4	0	6
6	0.528	0.038	10	2	10
7	1.056	0.076	6	4	15
8	1.584	0.115	10	2	71
9	2.112	0.153	10	6	69
10	2.640	0.191	8	2	83
11	3.168	0.229	13	6	92
12	4.224	0.306	15	4	90
13	5.280	0.382	25	0	85
14	6.336	0.459	38	0	69
15	8.448	0.612	69	6	33
16	16.896	1.224	73	10	8

[1] Brantom (1983); Peto *et al.* (1991a,b). Animals were provided, for their entire lives until natural death, drinking water containing the indicated concentrations of NDMA. The animals were sacrificed and necropsied if moribund or exhibiting palpable liver alterations.

[2] Intakes estimated by authors (Peto *et al.*, 1991b).

[3] Proportion of animals with tumours specified at each dose level; n = 192 for unexposed controls (treatment group 1); n = 48 for each dose level (treatment groups 2–16) (Brantom, 1983).

2.4.3.4 Genotoxicity

The results of numerous studies conducted *in vitro* with bacterial and mammalian cells have provided overwhelming evidence that NDMA is mutagenic and clastogenic (reviewed in IARC, 1978; ATSDR, 1989). Increased frequencies of gene mutations, chromosomal damage, sister chromatid exchange and unscheduled DNA synthesis have been observed in a wide variety of cell types, in assays conducted in the presence or absence of metabolic activation. Positive results have been observed in human as well as in rodent cells.

Similarly, clear evidence of genetic effects has also been observed in *in vivo* studies. Clastogenic effects (e.g., micronuclei, sister chromatid exchange, chromosomal aberrations) in hepatocytes (Tates *et al.*, 1980, 1983, 1986; Braithwaite and Ashby, 1988; Cliet *et al.*, 1989; Neft and Conner, 1989; Sawada *et al.*, 1991), bone marrow cells (Bauknecht *et al.*, 1977; Wild, 1978; Neal and Probst, 1983; CSGMT, 1986; Neft and Conner, 1989; Krishna *et al.*, 1990; Sato *et al.*, 1992; Morrison and Ashby, 1994), spleen cells (Neft and Conner, 1989; Krishna *et al.*, 1990), peripheral blood lymphocytes (Tates *et al.*,

1983; Sato *et al.*, 1992) and spermatids (Cliet *et al.*, 1993), as well as in esophageal (Mehta *et al.*, 1987) and kidney cells (Robbiano *et al.*, 1997), have been observed in rodents (rats, mice or hamsters) administered NDMA either orally or by intraperitoneal injection. The inhalation exposure of female mice to NDMA increased the frequency of micronucleated bone marrow cells (Odagiri *et al.*, 1986). Evidence of genotoxicity (e.g., chromosomal aberrations, micronuclei, gene mutation, DNA strand breaks) has also been observed in the offspring of hamsters (Inui *et al.*, 1979) and mice (Bolognesi *et al.*, 1988) administered NDMA during gestation.

In rodents (rats, mice or hamsters) administered NDMA either orally or by intraperitoneal injection, evidence of DNA damage has been observed in the liver, kidneys and lungs (Laishes *et al.*, 1975; Petzold and Swenberg, 1978; Abanobi *et al.*, 1979; Mirsalis and Butterworth, 1980; Brambilla *et al.*, 1981, 1987; Bermudez *et al.*, 1982; Cesarone *et al.*, 1982; Barbin *et al.*, 1983; Doolittle *et al.*, 1984; Kornbrust and Dietz, 1985; Loury *et al.*, 1987; Mirsalis *et al.*, 1989; Pool *et al.*, 1990; Brendler *et al.*, 1992; Jorquera *et al.*, 1993; Asakura *et al.*, 1994; Tinwell *et al.*, 1994; Webster *et al.*, 1996). DNA damage in thymus (Petzold and Swenberg, 1978), sperm (Cesarone *et al.*, 1979), and nasal and tracheal cells (Doolittle *et al.*, 1984) has also been noted. NDMA was mutagenic at the *lacI* locus (in the liver) in *in vivo* assays involving transgenic mice (Mirsalis *et al.*, 1993; Tinwell *et al.*, 1994; Butterworth *et al.*, 1998).

Exposure to NDMA may lead to the formation of methylated bases within the genome (see Section 2.4.3.7).

2.4.3.5 Reproductive and developmental toxicity

Available data on the reproductive or developmental toxicity of NDMA are limited primarily to results derived from older studies. In a report by Anderson *et al.* (1978), time to conception in female mice provided with drinking water containing 0.1 mg NDMA/L for 75 days prior to mating was about 3 days longer than in unexposed controls; no other reproductive effects were assessed in this study. In a study conducted with male rats, a single intraperitoneal injection of 30 or 60 mg NDMA/kg-bw induced testicular damage (necrosis or degeneration of the seminiferous epithelium) (Hard and Butler, 1970b).

In a single-generation study (Anderson *et al.*, 1978) in which the reproductive effects of a number of substances were examined, groups of 20 female mice were provided with drinking water containing 0 or 0.1 mg NDMA/L for 75 days prior to mating and throughout pregnancy and lactation (estimated daily and total intakes of 0.02 mg/kg-bw per day and 2 mg/kg-bw, respectively). The proportion of deaths (based upon the total number of stillborn and neonatal deaths) was increased ($p < 0.05$) 2-fold in the NDMA-exposed animals, compared with controls (i.e., 20% and 9.9%, respectively), due in large part to an increase in the number of stillborn animals. Exposure to NDMA had no effect upon maternal fluid consumption, litter size or average body weight of the weanlings, and no consistent gross or histopathological abnormalities were observed in the stillborn fetuses or dead neonates to account for the increased mortality. In a somewhat more recent study with mice administered higher doses of the nitrosamine, a single intraperitoneal injection of 37 mg NDMA/kg-bw on day 16 or 19 of gestation resulted in the deaths of the fetuses in all exposed dams; lethality was not observed following the administration of 7.4 mg NDMA/kg-bw (Anderson *et al.*, 1989).

Fetal body weight was significantly ($p < 0.05$) reduced after a single oral dose of 20 mg NDMA/kg-bw was administered to pregnant rats on day 15 or 20 of gestation (Nishie, 1983). Although information on fetal survival or teratogenicity was not provided, toxic effects (reduced weight gain, hepatotoxicity and

death) were observed among the dams. Fetal deaths were noted in a number of studies (cited in ATSDR, 1989) conducted with rats in which NDMA was administered to pregnant dams 1) as a single oral dose (30 mg/kg-bw) on one of days 1 12 (Alexandrov, 1974) or 1 15 (Napalkov and Alexandrov, 1968) of gestation; 2) as repeated gavage doses of 1.4 2.9 mg/kg-bw per day for 7 or more days during gestation (Napalkov and Alexandrov, 1968); or 3) in the diet (intake of 5 mg/kg-bw per day) from an unspecified day in early pregnancy to sacrifice on day 20 of gestation (Bhattacharyya, 1965). Although no teratogenic effects were reported in these studies, interpretation of these investigations is difficult owing to insufficient information on experimental design and results, lack of controls and lack of information on maternal toxicity (ATSDR, 1989).

2.4.3.6 Neurotoxicity and effects on the immune system

Data concerning effects on the brain or central nervous system in animals exposed to NDMA were not identified.

In studies in which B6C3F$_1$ female mice were administered repeated intraperitoneal injections of 1.5, 3 or 5 mg NDMA/kg-bw per day for 14 days, observed effects on the immune system included suppression of humoral immunity with declines in the IgM antibody-forming cell response to sheep red blood cells and reductions in splenocyte proliferation in response to lipopolysaccharide (reviewed in Haggerty and Holsapple, 1990). Also observed were reductions in T-lymphocyte function (i.e., reduced cell-mediated immunity) with a decline in proliferative responses to various T-cell mitogenic stimuli, suppression of the mixed lymphocyte response and selected delayed hypersensitivity responses, as well as significant reductions in host resistance to infection with *Listeria monocytogenes*, *Streptococcus zooepidemicus* or the influenza virus or to challenge with B16F10 tumour cells.

Female CD-1 mice provided with drinking water containing 5 or 10 mg NDMA/L for 30 120 days exhibited marked suppression of humoral- and cell-mediated immunity (Desjardins *et al.*, 1992). No effects were observed in animals consuming drinking water containing 1 mg NDMA/L.

2.4.3.7 Toxicokinetics and mode of action

Quantitative information on the absorption or distribution of NDMA following oral, inhalation or dermal exposure in humans was not identified. The development of severe effects following acute exposure to NDMA provides evidence that this nitrosamine is absorbed from the gastrointestinal tract and the lungs.

On the basis of studies conducted with laboratory animals, ingested NDMA is absorbed rapidly and extensively (Daugherty and Clapp, 1976; Diaz Gomez *et al.*, 1977; Kunisaki *et al.*, 1978), primarily from the lower intestinal tract (Phillips *et al.*, 1975; Hashimoto *et al.*, 1976; Agrelo *et al.*, 1978; Pegg and Perry, 1981). Detection of NDMA in the urine of rats and dogs exposed by inhalation indicates that the nitrosamine is absorbed through the lungs; however, reliable quantitative information on the absorption of NDMA following inhalation was not identified.

Once absorbed, NDMA and its metabolites are distributed widely (Daugherty and Clapp, 1976; Anderson *et al.*, 1986) and likely passed to offspring through mothers milk (Diaz Gomez *et al.*, 1986). The nitrosamine and its metabolites have been detected in the fetuses of pregnant rodents injected with the substance (Althoff *et al.*, 1977; Johansson-Brittebo and Tj ve, 1979). Pharmacokinetic analyses of NDMA injected intravenously into a number of laboratory species have revealed that the nitrosamine is cleared rapidly from the blood, with metabolism involving both hepatic and extrahepatic components. NDMA and its metabolites may be excreted in the urine or exhaled as carbon dioxide.

The metabolism of NDMA involves either the alpha-hydroxylation or denitrosation of the nitrosamine. Both pathways are considered to proceed through a common intermediate radical [$CH_3(CH_2\cdot)N–N=O$], generated by the action of the cytochrome P450[CYP2E1]-dependent mixed-function oxidase system (Haggerty and Holsapple, 1990; Lee *et al.*, 1996). Along the alpha-hydroxylation pathway, the hydroxymethylnitrosamine ($HOCH_2CH_3N–N=O$) formed from the intermediate radical decomposes to formaldehyde (itself ultimately converting to carbon dioxide) and monomethylnitrosamine ($CH_3NHN=O$); the monomethylnitrosamine, owing to its instability, undergoes rearrangement to the strongly methylating methyldiazonium ion ($CH_3N^+\equiv N$), which alkylates biological macromolecules such as DNA, RNA and proteins. Metabolic conversion of the intermediate radical via denitrosation may lead to the formation of methylamine (CH_3NH_2) and formaldehyde. There appear to be no qualitative differences in the metabolism of NDMA between humans and laboratory animals.

On the basis of *in vitro* assays conducted with rat hepatocyte cultures, Lee *et al.* (1996) attributed the hepatotoxicity of NDMA to the methyldiazonium ion formed via the alpha-hydroxylation pathway; denitrosation was considered to make little contribution to the overall hepatotoxic effect of this nitrosamine in rats. Available data provide strong evidence that the toxicological effects of NDMA are directly dependent upon the cytochrome P450[CYP2E1]-dependent metabolic conversion of this nitrosamine to highly reactive species; therefore, substances that alter the expression and/or activity of this protein might have an influence upon the toxicological effects exerted by NDMA (Yang *et al.*, 1991; Anderson, 1992; Tsutsumi *et al.*, 1993; Barcelo *et al.*, 1996; Encell *et al.*, 1996; Espinosa-Aguirre *et al.*, 1996, 1997; Shu and Hollenberg, 1996, 1997). Ethanol is a competitive inhibitor of the cytochrome P450[CYP2E1]-dependent metabolism of NDMA. Compared with studies in which laboratory animals were administered NDMA alone, the concurrent administration of the nitrosamine and ethanol has been shown to increase the bioavailability of NDMA (administered orally) in monkeys and mice (Anderson *et al.*, 1992a, 1994), the levels of the nitrosamine measured within the various tissues of mice (Anderson *et al.*, 1986), its residence time within the blood, liver and lungs in mice (Anderson *et al.*, 1994), the half-life for the elimination of NDMA (administered either intravenously or by gavage) from the blood in monkeys and mice (Anderson *et al.*, 1992a, 1994) and the amount of the nitrosamine eliminated in the urine of rats and monkeys (Swann *et al.*, 1984; Anderson *et al.*, 1992a).

Exposure to NDMA may lead to the formation of methylated bases within the genome. These methylation reactions occur after NDMA has been metabolized to the highly reactive methyldiazonium ion through the action of microsomal cytochrome P450[CYP2E1]-dependent mixed-function oxidase. The principal DNA adduct formed following exposure to NDMA is *N*^{7}-methylguanine (representing about 65% of all adducts formed initially upon exposure); *O*^{6}-methylguanine is a secondary adduct (representing about 7% of all adducts formed initially). Other DNA adducts formed in smaller amounts include *N*^{3}-methyladenine and *O*^{4}-methylthymine.

Data indicate that there may be quantitative age- and species-related differences in the formation of *O*^{6}-methylguanine following exposure to NDMA, possibly linked to the activity of *O*^{6}-methylguanine DNA-methyltransferase, the enzyme involved in the repair of such lesions. In a study in which a single dose of 7 mg [^{14}C]NDMA/kg-bw was injected intraperitoneally into newborn and adult Swiss Webster mice, higher amounts of hepatic *O*^{6}-methylguanine were measured in the newborns than in the adults (Coccia *et al.*, 1988). Notably, hepatic *O*^{6}-methylguanine DNA-methyltransferase activity was greater in the

adults than in the newborns. In an earlier study (Lindamood *et al.*, 1984) in which F344 rats and C3H or C57BL mice were provided drinking water containing 10, 30 or 100 mg NDMA/L for 16 days, hepatic O^6-methylguanine DNA-methyltransferase activity was increased in the rats but reduced in the mice receiving NDMA. The levels of this DNA adduct in the liver were higher in mice than in rats. A comparison of the two mouse strains revealed a greater accumulation of O^6-methylguanine in hepatocytes from C3H mice than in hepatocytes from C57BL mice. In mice, the formation of O^6-methylguanine DNA adducts within the lungs was increased markedly when the animals were administered (intragastrically) NDMA and ethanol, compared with the nitrosamine alone (Anderson, 1992).

The influence of dietary constituents on hepatic DNA methylation by NDMA was examined by Camus *et al.* (1990). These authors observed a 6-fold higher level of O^6-methylguanine in the livers of rats administered NDMA in a high-fat diet for 6 weeks, compared with animals receiving the same amount of the nitrosamine in a low-fat diet.

In monkeys administered (orally) 0.1 mg NDMA/kg-bw, O^6-methylguanine was detected in 32 tissues examined (Anderson *et al.*, 1996). The highest levels were in the gastric mucosa and liver, but elevated levels were also present in white blood cells, the esophagus, ovaries, pancreas, bladder and uterus. O^6-Methylguanine DNA-methyltransferase activity varied over a 30-fold range; the highest activities were in the gastric mucosa, liver, kidneys and lungs. Levels of O^6-methylguanine in a variety of tissues were higher following co-exposure with ethanol (Anderson *et al.*, 1995, 1996). The formation of O^6-methylguanine was detected in fetal liver, lung, kidney, spleen and brain in a study in which pregnant patas monkeys were administered (intragastrically) a single dose of 1 mg NDMA/kg-bw (Chhabra *et al.*, 1995).

The mutagenic and carcinogenic activities of NDMA are believed to be mediated (in part) by the methylation of specific bases within the genome. Although there appears to be no direct relationship between the formation of N^7-methylguanine and tumour development, the formation and persistence of O^6-methylguanine have been shown to be associated with both the carcinogenicity and mutagenicity of NDMA (reviewed in Haggerty and Holsapple, 1990; Swenberg *et al.*, 1991; Souliotis *et al.*, 1995). The ability of cells to repair such DNA adducts (by removing O^6-methylguanine through the action of a specific O^6-methylguanine DNA-methyltransferase) prior to cell division likely plays a critical role in determining the susceptibility of tissues to tumour development.

N^7-Methylguanine may undergo depurination yielding apurinic sites, which, if not repaired prior to DNA replication, can result in guanine to thymine transversions (Swenberg *et al.*, 1991). O^6-Methylguanine and O^4-methylthymine (formed at about 1% of the amount of O^6-methylguanine) are strongly promutagenic by direct mispairing. O^6-Methylguanine gives rise to guanine:cytosine to adenine:thymine (i.e., G:C to A:T) transitions, while O^4-methylthymine causes A:T to G:C transitions (Swenberg *et al.*, 1991; Souliotis *et al.*, 1995). The greater persistence of O^6-methylguanine DNA adducts in the kidney compared with the liver in rats administered a single oral dose of 20 mg NDMA/kg-bw parallels earlier findings in which the acute oral or intraperitoneal administration of NDMA to rats at such dose levels increased the incidence of kidney but not liver tumours (Magee and Barnes, 1962; Schmidt and Murphy, 1966; Hard and Butler, 1970a; McLean and Magee, 1970). In contrast, the long-term oral administration of low doses of NDMA (i.e., <2 mg/kg-bw per day) increases the incidence of liver but not kidney tumours in these animals (Brantom, 1983; Lijinsky and Reuber, 1984; Peto *et al.*, 1991a,b), a finding attributed to the first-pass metabolism of NDMA in the liver (Swenberg *et al.*, 1991).

Evidence supporting a role for O^6-methylguanine formation in tumour development following exposure to NDMA was recently reviewed by Souliotis *et al.* (1995). G:C to A:T transitions have been observed in the *ras* oncogene in mouse lung tumours induced by NDMA (Devereux *et al.*, 1991), in the livers of *lacI* transgenic mice administered a single dose of 4 mg NDMA/kg-bw (Mirsalis *et al.*, 1993) and in the liver, kidney and lung of *lacI* transgenic mice administered five daily doses of 1 mg NDMA/kg-bw (Wang *et al.*, 1998). Moreover, transgenic mice expressing high levels of O^6-methylguanine DNA-methyltransferase in the liver were less susceptible than normal controls to NDMA-induced hepatocarcinogenesis (Nakatsuru *et al.*, 1993). However, Souliotis *et al.* (1995) also reported that the dose–response relationship for the accumulation of O^6-methylguanine in hepatic DNA in rats administered drinking water (for 28 days) containing concentrations of NDMA similar to those used in the study conducted at BIBRA Toxicology International (Brantom, 1983; Peto *et al.*, 1991a,b) did not strictly parallel the dose–response for the development of hepatic tumours in the carcinogenicity bioassay.

2.4.4 *Humans*

Two deaths linked to the acute ingestion of NDMA, as well as a third attributed to the consumption of at least four doses of approximately 250–300 mg NDMA over a 2-year period, have been reported (Fussgänger and Ditschuneit, 1980; Pedal *et al.*, 1982). Liver failure was observed in all three cases; the two acutely exposed decedents also exhibited cerebral hemorrhage. In two fatalities involving exposure to unknown concentrations of NDMA fumes, a tender and enlarged liver, splenic enlargement, abdominal distension and the accumulation of yellow fluid in the peritoneal cavity were observed in one man prior to death (Freund, 1937); in the other death, liver cirrhosis was observed at autopsy (Hamilton and Hardy, 1974). In two other non-fatal cases involving exposure to NDMA fumes, effects included jaundice, the accumulation of fluid in the peritoneal cavity, exhaustion, headaches, abdominal cramps, soreness on the left side, nausea and vomiting (Freund, 1937; Hamilton and Hardy, 1974).

Relevant epidemiological studies include case–control investigations in which the potential risks of cancer of the stomach (Risch *et al.*, 1985; González *et al.*, 1994; Pobel *et al.*, 1995), upper digestive tract (Rogers *et al.*, 1995) and lung (Goodman *et al.*, 1992; De Stefani *et al.*, 1996) associated with the ingestion of NDMA have been assessed. Exposure-related increased risks of stomach cancer (González *et al.*, 1994; Pobel *et al.*, 1995), oral, laryngeal and esophageal cancers (Rogers *et al.*, 1995) and lung cancer (Goodman *et al.*, 1992; De Stefani *et al.*, 1996) have been reported; however, the trends were not always statistically significant. Moreover, in some of these reports (Goodman *et al.*, 1992; González *et al.*, 1994; Pobel *et al.*, 1995), the estimated intake of NDMA was based upon recollection of an individual's typical diet consumed in the year preceding the onset of illness, as well as the reported levels of this nitrosamine in the foodstuffs consumed, derived from other studies. In the studies conducted by De Stefani *et al.* (1996) and Rogers *et al.* (1995), subjects were asked to recall their typical diet in the 5 and 10 years, respectively, prior to the onset of illness. Other factors (e.g., other dietary constituents; occupational exposures) may also contribute to the increased risks observed in these studies.

There appears to be no qualitative difference between rodents and humans in the formation of DNA adducts following exposure to NDMA. In a case of suspected NDMA poisoning in a human male, methylation of liver DNA was evident at both the N^7- and O^6-positions of guanine (Herron and Shank, 1980). Using an immunohistochemical technique, Parsa *et al.* (1987) detected the formation of O^6-methylguanine in human pancreatic explants incubated *in vitro* with NDMA.

3.0 ASSESSMENT OF "TOXIC" UNDER CEPA 1999

3.1 CEPA 1999 64(a): Environment

The environmental risk assessment of a PSL substance is based on the procedures outlined in Environment Canada (1997a). Environmental assessment endpoints (e.g., adverse reproductive effects on sensitive fish species in a community) are selected based on analysis of exposure pathways and subsequent identification of sensitive receptors. For each endpoint, a conservative Estimated Exposure Value (EEV) is selected and an Estimated No-Effects Value (ENEV) is determined by dividing a Critical Toxicity Value (CTV) by an application factor. A conservative (or hyperconservative) quotient (EEV/ENEV) is calculated for each of the assessment endpoints in order to determine whether there is potential ecological risk in Canada. If these quotients are less than one, it can be concluded that the substance poses no significant risk to the environment, and the risk assessment is completed. If, however, the quotient is greater than one for a particular assessment endpoint, then the risk assessment for that endpoint proceeds to an analysis where more realistic assumptions are used and the probability and magnitude of effects are considered. This latter approach involves a more thorough consideration of sources of variability and uncertainty in the risk analysis.

3.1.1 Assessment endpoints

Since NDMA is not persistent in the environment, environmental effects are most likely to occur near point sources. Results of various industry and municipal surveys indicate that most releases of NDMA are to water. When NDMA is released to water, nearly all of it remains and reacts in the water phase. Based on NDMA's short half-life in air and the amounts being released to air, it is unlikely that effects will occur on wildlife near point sources. Since there are no detectable releases to sediment and soil, and as NDMA does not move from water to these compartments, they do not appear to be of concern. Therefore, the assessment of NDMA released to water focusses on organisms exposed in water near point sources.

3.1.1.1 Assessment endpoints for releases to water

Assessment endpoints include abundance and survival of fish, invertebrates, amphibians and algae. These organisms are an integral part of ecosystems, as each trophic level provides food for higher levels in the aquatic food chain. For example, algae are primary producers, forming the base of the food chain. Phytoplankton abundance and productivity are important to aquatic ecosystems, because phytoplankton provides food for a variety of planktivorous organisms and thus controls energy flow in a portion of the ecosystem. Cladocerans such as *Daphnia magna* consume bacteria and phytoplankton and are themselves consumed by many fish species. Various fish species feed on aquatic vegetation, phytoplankton, zooplankton, benthic invertebrates, benthic vertebrates, etc. Vertebrate omnivores provide food for vertebrate carnivores. The most sensitive measurement endpoint identified for aquatic species was growth of the green alga (*Selenastrum capricornutum*).

As NDMA is a potent inducer of acute toxic and chronic neoplastic lesions in aquatic species, assessment endpoints reflecting these effects are mentioned here. Nearly all of the studies conducted on a variety of species at different trophic levels have shown tumour formation as a result of exposure to NDMA. Although a tumorigenic endpoint is not traditionally used as an indicator of a population-

level effect, it may have implications if an endangered species is found in the area of discharge of effluent containing NDMA. At this time, however, implications of tumour induction in environmental species are unclear.

3.1.2 Environmental risk characterization

3.1.2.1 Aquatic organisms

Based on the sources and fate of NDMA, and because data on concentrations in ambient water near point sources are not available, end-of-pipe concentrations in final effluent were used as a measure of exposure to aquatic organisms. Recent concentrations have been selected to reflect present exposures. The highest concentration of NDMA in wastewater discharged to a water body was 0.266 µg/L. Although this concentration is expected to decrease, as the company installed a wastewater treatment plant in early 1998, this value is used as the EEV in the hyperconservative analysis of chronic exposure for aquatic plants and animals.

For chronic exposure of aquatic organisms to NDMA, the CTV is 4000 µg/L, based on a 13-day EC_{50} for inhibition of growth in the green alga (*Selenastrum capricornutum*). This value was selected from a data set composed of several studies conducted on at least eight species of aquatic organisms, which include phytoplankton, zooplankton, fish, amphibians and invertebrates. It is important to note that in the second most sensitive study, tumours were found in the organism. Khudoley (1977) reported that liver tumours were induced in 44% of frogs (*Rana temporaria*) after 203 days of exposure at a concentration of 5000 µg/L. Again, as was indicated in Section 3.1.1.1, the implications of tumour induction as a population-level effect cannot be determined at this time.

For a hyperconservative analysis, the ENEV is derived by dividing the CTV by a factor of 100. This accounts for the uncertainty surrounding the conversion of a short-term EC_{50} to a chronic no-effects value, the extrapolation from laboratory to field conditions, and interspecies and intraspecies variations in sensitivity. As a result, the ENEV is 40 µg/L.

The hyperconservative quotient is calculated by dividing the EEV of 0.266 µg/L by the ENEV for green algae as follows:

$$\text{Quotient} = \frac{\text{EEV}}{\text{ENEV}}$$

$$= \frac{0.266\ \mu g/L}{40\ \mu g/L}$$

$$= 0.007$$

Since the hyperconservative quotient is less than one, it is unlikely that NDMA releases will cause adverse effects on populations of aquatic organisms in Canada.

3.1.2.2 Discussion of uncertainty

There are a number of sources of uncertainty in this environmental risk assessment. Concentrations of NDMA in some areas in Canada could be higher than those identified and used in this assessment. While no or limited data were identified for Canadian soil, sediments and air, NDMA is not expected in these compartments or would be present at extremely low concentrations, because of the absence of sources to these media and the unlikely partitioning of NDMA to these compartments from water. There were adequate data identified on concentrations of NDMA in water near industrial point sources, such as rubber chemical manufacturers. However, the data used in this assessment are considered acceptable because they were selected from recent water monitoring studies that included sites of known contamination located in southwestern Ontario. Point sources are expected to have the highest NDMA emissions due to the presence of NDMA precursors in the effluent and in the receiving waters.

Regarding effects of NDMA on aquatic organisms, there is uncertainty in the extrapolation from available toxicity data to potential ecosystem effects. The toxicity data set for aquatic biota, however, is considered adequate, as it includes a variety of species from different trophic levels. While some of the studies are relatively old (1960s to 1980s), they are generally of good quality and are considered acceptable for the assessment. To counter uncertainties in extrapolation, an appropriate application factor was used in the environmental risk analysis to derive an ENEV.

3.2 CEPA 1999 64(b): Environment upon which life depends

The estimated potential contribution of NDMA to stratospheric ozone depletion, to ground-level ozone formation and to climate change is negligible. Both the GWP and the POCP are overestimated. In addition, the environmental impact of NDMA emissions to the atmosphere will be much smaller than that of the ozone-forming reference compound ethene, because much smaller quantities of NDMA are emitted.

3.3 CEPA 1999 64(c): Human health

3.3.1 Estimated population exposure

Data on levels of NDMA in environmental media in Canada to serve as a basis for development of estimates of population exposure are limited in both spatial and temporal scope. Monitoring of NDMA in food in Canada was more intensive in the 1970s and 1980s than in more recent periods. Surveys of NDMA in ambient air (primarily in the vicinity of point sources) in Canada have been conducted only in Ontario in the early 1990s. Similarly, data on concentrations of NDMA in drinking water are available only for Ontario, although this information is available for the 1990s and is ongoing. Among consumer products, there have been periodic surveys of the NDMA content of rubber baby bottle nipples and pacifiers in Canada from the early 1980s to the present. In contrast, no Canadian data were identified on concentrations of NDMA in indoor air, personal care products (e.g., cosmetics) or tobacco products, although for cosmetics, notifications of products with levels exceeding 10 µg nitrosamines/kg are precluded.

Point estimates of daily intake (per kilogram body weight), based on these few data and reference values for body weight, inhalation volumes and amounts of food and drinking water consumed daily, are presented for six age groups in Table 4. These are ranges of reasonable worst-case estimates of daily intake, based on historic data, and indicate that daily intake of NDMA may be as high as 0.03 µg/kg-bw per day. It is not possible to develop defensible estimates of the current average daily intakes of NDMA for the general population due to the limitations of the (particularly recent) available Canadian data. If, despite these limitations, the lower ends of the ranges of reasonable worst-case estimates are considered upper bounds of average population exposure estimates, the daily intake of NDMA from outdoor air (in the vicinity of point sources), water and food for the general population is unlikely to exceed 0.008 µg/kg-bw per day. Based on the assumptions underlying the reasonable worst-case estimates, most of the daily intake can be attributed to consumption of food contaminated with NDMA during processing, preservation and/or preparation. It should be noted, though, that the early data on which the estimates in food are based may not be representative of the situation today, due to the impact of subsequent introduction of changes in food processing and controls to limit formation in food. Intake of NDMA due to inhalation of air contaminated by atmospheric discharges from industrial point source contributes somewhat less

TABLE 4 Reasonable worst-case estimates of daily intake of NDMA by the general population in Canada

Media	Reasonable worst-case estimates of daily intake of NDMA (µg/kg-bw per day)					
	0–0.5 years[1]	0.5–4 years[2]	5–11 years[3]	12–19 years[4]	20–59 years[5]	60+ years[6]
Air[7]	0.0005–0.005	0.001–0.011	0.0008–0.009	0.0004–0.005	0.0004–0.004	0.0003–0.004
Water[8]	0.0013–0.004	0.0006–0.002	0.0004–0.001	0.0002–0.001	0.0003–0.001	0.0003–0.001
Food[9,10]	0.0004–0.001[11]	0.0065–0.016	0.0045–0.011	0.0036–0.009	0.0043–0.011	0.0036–0.009
Subtotals	0.0022–0.010[12]	0.0081–0.029	0.0057–0.021	0.0042–0.015	0.005–0.016	0.0042–0.014
Indoor air–ETS[13]	0.06	0.13	0.10	0.06	0.05	0.04
Groundwater[14]	0.14–0.31	0.06–0.13	0.05–0.10	0.03–0.06	0.03–0.06	0.03–0.06
Beer[15]				<0.0002	0.0009	<0.0004
Shampoo[16]				0.000 02	0.000 02	0.000 02

[1] Assumed to weigh 7.5 kg, to drink 0.8 L/day of total tap water (as infant formula) and to breathe 2.1 m^3 of air per day (EHD, 1998).

[2] Assumed to weigh 15.5 kg, to drink 0.7 L/day of total tap water and to breathe 9.3 m^3 of air per day (EHD, 1998).

[3] Assumed to weigh 31.0 kg, to drink 1.1 L/day of total tap water and to breathe 14.5 m^3 of air per day (EHD, 1998).

[4] Assumed to weigh 59.4 kg, to drink 1.2 L/day of total tap water and to breathe 15.8 m^3 of air per day (EHD, 1998).

[5] Assumed to weigh 70.9 kg, to drink 1.5 L/day of total tap water and to breathe 16.2 m^3 of air per day (EHD, 1998).

[6] Assumed to weigh 72.0 kg, to drink 1.6 L/day of total tap water and to breathe 14.3 m^3 of air per day (EHD, 1998).

[7] These reasonable worst-case estimates of intake by inhalation are based on short-term measurements of NDMA in outdoor air in the close vicinity of point sources of atmospheric discharge in Ontario. The minimum estimates are based on the lowest limit of detection (i.e., 0.0017 µg/m^3) for half-hour averaging times for Trace Atmospheric Gas Analyser (TAGA) measurements of NDMA in Kitchener, Ontario, in 1992 (OME, 1992a). The maximum estimates are based on the censored mean concentration (i.e., 0.019 µg/m^3) for half-hour averaging times for TAGA measurements of NDMA (n = 74) in Elmira and Kitchener, Ontario (OME, 1990, 1992a). Concentrations equivalent to one-half the appropriate limits of detection were assumed for half-hour averages during which NDMA was not detected. It was assumed that the population would be exposed to similar concentrations for 24 hours daily, and that concentrations in the indoor air would be the same as those in outdoor air, in the immediate vicinity of the point sources.

[8] These reasonable worst-case estimates of intake by ingestion of drinking water are based on concentrations of NDMA measured in drinking water in Ontario. The minimum estimates are based on the mean concentration (i.e., 0.012 µg/L) for 20 samples from four water treatment plants in Ontario where elevated concentrations of NDMA were attributed to the use of a pre-blended polyamine/alum product in the water treatment plant (OMEE, 1996). The maximum estimates are based on the maximum concentration (i.e., 0.04 µg/L) among these 20 samples, measured at the water treatment plant in Huntsville, Ontario (OMEE, 1996).

[9] Daily consumption rates (i.e., grams/person per day) of 181 food items by six age groups of Canadians (EHD, 1998) are the basis for the calculation of the reasonable worst-case daily intake of NDMA from ingestion of foods. In Canada, NDMA has been detected in 10 food items for which these daily consumption rates are available. (Intakes from an 11th food item [i.e., beer] are not included in these intake estimates.) The maximum concentrations of NDMA reported for each of the 10 food items (Sen *et al.*, 1978, 1979, 1980b, 1985) were selected for calculation of the maximum estimates of intake from foods for the six age groups. Concentrations of NDMA in the remaining 171 were assumed to be zero.

[10] The maximum concentrations in each of the 10 food items (i.e., referred to in footnote 9) were reduced in proportion to the frequencies of detection of NDMA in the food item for calculation of the minimum estimates of intake from foods for the six age groups (EHD, 1998). The number of samples of each of the 10 food items referred to in footnote 9 ranged from 2 (for cottage cheese) to 55 (for cured pork). The frequencies of detection of NDMA in the 10 food items were calculated and ranged from 25% to 100%. Concentrations of NDMA in the remaining 171 food items were assumed to be zero.

[11] The estimates of intake of NDMA by infants were based on the assumption that these infants consume table-ready foods at rates indicated in EHD (1998).

[12] The total daily intake of NDMA by infants is overestimated, since the infants are assumed to be consuming both formula (i.e., reconstituted with drinking water) and table-ready foods on a daily basis.

[13] Based on the assumption that the population spends 21 hours per day (EHD, 1998) breathing ETS-contaminated indoor air containing NDMA at the maximum reported concentration (0.24 µg/m^3) measured in a bar in the United States (Brunnemann and Hoffmann, 1978).

[14] Based on the minimum (1.3 µg/L) and maximum (2.9 µg/L) concentration of NDMA in well water in Elmira, Ontario (ECO LOGIC, 1989), resulting from contamination of groundwater by a nearby industrial facility, and average daily rates of water consumption (EHD, 1998).

[15] Based on the most recent maximum concentration (0.59 µg/L) of NDMA in Canadian beer (Sen *et al.*, 1996) and average daily rates of intake of beer from EHD (1998).

[16] Dermal intake only. These estimates are based on the Canadian regulatory limit (i.e., 10 µg/kg) for nitrosamines in personal care products (Green, 1995). Shampoo was selected, as the maximum reported concentration of NDMA (24 µg/kg) in such products has been in shampoo, in Germany (Spiegelhalder and Preussmann, 1984). Dermal intake was estimated by a generalized approach involving product use scenarios (ECETOC, 1994).

to the total daily intake,[2] and an even smaller contribution is attributed to consumption of drinking water containing NDMA, based on a survey of water treatment plants in Ontario. However, although possibly unrepresentative, available data indicate that contaminated groundwater in the vicinity of industrial point sources can, in some cases, lead to intakes that are greater than those from all other media combined.

No data were identified concerning concentrations of NDMA in non-workplace indoor air in Canada. NDMA is one of a number of *N*-nitrosamines present in cigarette smoke and ETS. Concentrations of NDMA in ETS-contaminated indoor air in other countries have ranged as high as 0.24 µg/m^3. If it is assumed that the population is exposed to this maximum concentration in indoor air for 21 hours per day (EHD, 1998), the upper-bounding estimates of intake by inhalation range from 0.04 to 0.13 µg/kg-bw per day.

No data were identified concerning the concentrations of NDMA in the mainstream smoke of cigarettes in Canada. Data from the United States indicate that mainstream smoke may contain between 4 ng/cigarette (Adams *et al.*, 1987) and 278 ng/cigarette (Kataoka *et al.*, 1997). If it is assumed that an average adult smoker consumes 20 cigarettes a day, the estimated intake of NDMA is 0.080–5.6 µg/smoker per day, or 0.001–0.08 µg/kg-bw per day. The upper end of this range of estimates of daily intake for smokers (i.e., 0.08 µg/kg-bw per day) is 5 times greater than the upper end of the range of reasonable worst-case estimates of intakes for adults from air, water and food (i.e., 0.016 µg/kg-bw per day, as summarized in Table 4).

Reasonable worst-case estimates of daily intake of NDMA for all age groups from ingestion of contaminated groundwater range from 0.03 to 0.31 µg/kg-bw per day (see Table 4). These estimates are based on the minimum (i.e., 1.3 µg/L) and maximum (i.e., 2.9 µg/L) confirmed concentrations of NDMA in supply wells in Elmira, Ontario, in 1989 (ECO LOGIC, 1989). The groundwater was contaminated by discharges from a nearby industrial facility.

Estimates of daily intake of NDMA from ingestion of beer are not included in the reasonable worst-case estimates of intakes from food in Table 4. For comparison, the most recent maximum concentration (i.e., 0.59 µg/L) of NDMA in Canadian beer (Sen *et al.*, 1996) and average daily rates of consumption of beer (EHD, 1998) are the basis for reasonable worst-case estimates of daily intake, which range from <0.0002 to 0.0009 µg/kg-bw per day.

Based on the limit (i.e., 10 µg/kg) for nitrosamines in cosmetics in Canada (Green, 1995), the potential dermal intake of NDMA from a shampoo was estimated based on product use scenarios (ECETOC, 1994). A shampoo was selected for this calculation, as the maximum reported concentration (i.e., 24 µg/kg) of NDMA in personal care products was in a shampoo in Germany (Spiegelhalder and Preussmann, 1984). The estimated intake of 0.000 02 µg/kg-bw per day resulting from this calculation (Health Canada, 1999) is several orders of magnitude less than the reasonable worst-case estimates of combined daily intakes from air, water and food that are summarized in Table 4.

3.3.2 Hazard characterization

Available data are consistent with the toxicological effects of NDMA being due, in large part, to the alkylation of biological macromolecules (e.g., DNA, RNA, proteins) by the methyldiazonium ion formed during metabolism. Putative pathways for the metabolism of NDMA are similar in rodents and humans.

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[2] Since NDMA was not detected in the one available survey of air not impacted by industrial point sources (i.e., Windsor, Ontario) (OME, 1994b), data were considered inadequate as a basis for estimation of the intake of NDMA in ambient air by the general population residing in an urban area, without point sources.

3.3.2.1 Carcinogenicity

Information relevant to assessment of the carcinogenicity of NDMA has been derived from epidemiological (case control) studies of the general population, carcinogenesis bioassays involving laboratory animals, as well as supporting data related to the genotoxicity, metabolism and interaction of this compound with biological macromolecules.

Although the database is rather limited, data from epidemiological studies are at least suggestive of an association between exposure to NDMA and several forms of cancer (i.e., gastric and lung). In two of three case control studies, there was a positive relationship with evidence of exposure response for the intake of NDMA and gastric cancer (GonzÆlez *et al.*, 1994; Pobel *et al.*, 1995), although not in an additional study in which oral, laryngeal and esophageal cancers were investigated separately (Rogers *et al.*, 1995). In two recent case control studies in which matching or control for confounders was rather more extensive than that for the investigations of gastric cancer mentioned above, there were clear exposure response relationships for NDMA and lung cancer (Goodman *et al.*, 1992; De Stefani *et al.*, 1996). In almost all studies, associations between the cancers of interest and nitrate, nitrite and NDMA were examined; results were relatively consistent in this regard, with there being an association with cancer most commonly with NDMA; results for nitrite were mixed, and nitrate generally had a protective effect. Although estimated intakes in these investigations were based on dietary recall, and although confounding factors such as alcohol were not accounted for, the data fulfil, at least in part, some of the traditional criteria for causality of an association between ingestion of NDMA and cancer.

Although, with the exception of a very extensive recent study, the available carcinogenesis bioassays for NDMA were conducted early and are considered quite limited by today s standards, the weight of evidence of the carcinogenicity of NDMA in mammalian species is consistent and convincing. Moreover, the pattern of tumour development is characteristic of that for a mode of action of carcinogenesis involving direct interaction with genetic material. In available studies, NDMA has induced tumours in all species examined (mice, rats, hamsters), at relatively low doses in some cases, irrespective of the route of exposure (oral, inhalation); tumours were induced in a wide range of tissues, including the liver, Leydig cells, lungs, kidney and nasal cavity, in the absence of significant non-neoplastic effects, in the limited number of studies in which these were well examined. Where it was reported, time to first tumour was relatively short. The incidence of specific tumours has been increased following administration of even a single dose or repeated doses for short periods (i.e., 2 3 weeks); tumours have also been observed in the offspring of exposed pregnant rats and mice.

NDMA has been consistently mutagenic and clastogenic in human and rodent cells exposed *in vitro*. Clear evidence of genetic effects has also been observed in a number of tissues from animals exposed to this substance. Notably, genotoxic effects have been observed in tissues (i.e., liver, kidney, lung) where tumours commonly arise following experimental exposure to NDMA.

While the mechanism by which NDMA induces tumours is not fully elucidated, DNA adducts (in particular, O^6-methylguanine) formed by the methyldiazonium ion generated during the metabolism of this nitrosamine likely make a significant contribution to its carcinogenicity. The importance of metabolism in mediating the toxicological effects of NDMA is illustrated by increases in O^6-methylguanine upon co-exposure to ethanol, a competitive inhibitor of the cytochrome P450-dependent mixed-function oxidase system. Levels of this putatively important adduct are higher in newborns than in adult animals exposed to similar levels of NDMA, likely due to the lower activity of

O^6-methylguanine DNA-methyltransferase in young animals; levels are also higher in animals consuming high-fat diets. Putative pathways for the metabolism of NDMA are similar in rodents and humans, and indeed the formation of O^6-methylguanine has been detected in human tissues exposed to NDMA.

Therefore, owing to the considerable evidence of carcinogenicity of NDMA in laboratory species, evidence of direct interaction with DNA consistent with tumour formation, as well as the apparent lack of qualitative species-specific differences in the metabolism of this substance, NDMA is highly likely to be carcinogenic to humans.

3.3.2.2 Non-neoplastic effects

Information on adverse health effects other than cancer in humans associated with exposure to NDMA is limited. In case reports, liver failure, brain hemorrhage and death have been attributed to the ingestion of NDMA. Effects resulting from exposure to unspecified amounts of airborne NDMA have included an enlarged liver and spleen, hepatic cirrhosis, jaundice, ascites as well as death.

Data on non-neoplastic effects in laboratory animals associated with exposure to NDMA are also limited, attributable primarily to the focus on its carcinogenicity. Effects on the liver and kidney in early repeated-dose toxicity studies, embryo toxicity and embryo lethality in early, single-dose developmental studies and a range of immunological effects (suppression of humoral and cell-mediated immunity) reversible at lowest concentrations have been reported.

3.3.3 Exposure–response analysis

The principal route of human exposure to NDMA for the general population, including those exposed in the vicinity of point sources, is ingestion. Moreover, information on exposure–response for the critical endpoint following inhalation and dermal exposure to NDMA is limited. Therefore, quantitation of dose–response is limited here to exposure via ingestion.

Scaling for variations in the ratios of surface area to body weight between rodent species and humans was not considered appropriate for the measures of exposure–response developed on the basis of experimental data in animals, since it is highly probable that the carcinogenicity of NDMA is mediated primarily through the generation of an active metabolite (i.e., the methyldiazonium ion).

3.3.3.1 Carcinogenicity

Cancer is clearly the critical endpoint for quantitation of exposure–response for risk characterization of NDMA. This has been the best characterized endpoint for this substance. Moreover, in general, tumours occur at lowest concentration, compared with those typically reported to induce non-cancer effects. An increased incidence of hepatic tumours was observed at doses as low as approximately 0.1 mg/kg-bw per day in rats, and the genotoxicity of NDMA (including formation of putatively critical adducts with DNA), for which the weight of evidence is exceedingly consistent and convincing, undoubtedly plays a critical role in tumour induction. A 2-fold increase in stillbirths and neonatal deaths (combined) was observed in mice receiving an estimated daily intake of 0.02 mg NDMA/kg-bw per day for 75 days prior to mating and throughout pregnancy and lactation. However, exposure to NDMA had no effect upon maternal fluid consumption, litter size or average body weight of the weanlings, and there were no consistent gross or histopathological abnormalities in the stillborn fetuses or dead neonates to account for the increased mortality. Moreover, increased mortality was not observed in another study in which mice were administered higher doses of the nitrosamine (i.e., a single intraperitoneal injection of 7.4 mg

NDMA/kg-bw on day 16 or 19 of gestation) (Anderson *et al.*, 1989).

Quantitation of exposure–response for cancer for NDMA is based on studies in laboratory animals, since existing epidemiological data, although suggestive of a possible association between ingestion of NDMA and cancer, are inadequate to serve as a basis for characterization of exposure–response. There appear to be no *qualitative* differences in metabolism of NDMA between humans and laboratory animals, and there is no reason to believe that humans would respond qualitatively differently.

By far the most suitable study for exposure–response analyses of the carcinogenic effects of NDMA is that reported by Brantom (1983) and Peto *et al.* (1991a,b), which involved the administration of NDMA in drinking water to a large number (n = 15) of large dose groups (n = 60) of male and female rats. Other available bioassays were early and considerably more limited — i.e., single dose groups, small group sizes and histopathological examination often restricted to one tissue.

The Tumorigenic Dose$_{05}$ (TD_{05}; i.e., the dose level that causes a 5% increase in tumour incidence over background) was calculated by first fitting the multistage model to the dose–response data. The multistage model is given by

$$P(d) = 1 - e^{-q_0 - q_1 d - \ldots - q_k d^k}$$

where d is dose, k is the number of dose groups in the study minus one, $P(d)$ is the probability of the animal developing a tumour at dose d and $q_i > 0$, $i = 1,\ldots,k$ are parameters to be estimated. TD_{05}s were then calculated as the dose D that satisfies

$$\frac{P(D) - P(0)}{1 - P(0)} = 0.05$$

A chi-square lack of fit test was performed for each of the three model fits. The degrees of freedom for this test are equal to k minus the number of q_i's for which estimates are non-zero. A p-value less than 0.05 indicates a significant lack of fit.

The study reported by Brantom (1983) and Peto *et al.* (1991a,b) contained 15 dose groups and controls, which is unusually large. Upper dose groups for which there was downturn in the dose–response curve were first eliminated from calculations of the TD_{05}. These dose groups add no information to the shape of the dose–response curve in the range of the TD_{05} and contribute to lack of fit of the model. In addition, extreme downturn is likely a sign that animals are dying of some other cause before having a chance to develop the tumour of interest.

Two methods were used to fit models to the large number of dose groups. In the first method, quadratic models (i.e., models with $k = 2$) were fit to the full set of data, less any dose groups contributing to downturn at the upper end of the dose–response curve. Any model with k larger than 2 did not converge when fitting models to the full data set. The second method involved reducing the number of dose groups to 10 (or less) by first eliminating upper dose groups with downturn and then collapsing adjacent similar dose groups together. Collapsing was accomplished by averaging the dose level and totalling the number of tumours for the two groups. Global82 (Howe & Crump, 1982) was then used to fit full multistage models to the reduced data. With the exception of biliary cystadenomas in females, these models did not show significant lack of fit. However, they generally appeared to overestimate the risk in the range of the TD_{05}, resulting in TD_{05} values that might be overly conservative. There was no evidence of a dose–response relationship for hemangiosarcomas in females; these data were not modelled, therefore, for the purpose of calculating a TD_{05}.

After reducing the data to 10 dose groups, the multistage model still occasionally exhibited lack of fit, due in large part to a levelling off of the dose–response relationship at higher doses. Since a good fit in the range of the TD_{05} is

required, upper dose groups were systematically eliminated until a reasonable fit was achieved. The data finally used to compute TD_{05}s for hepatic tumours in the male and female rats from the Brantom (1983) and Peto *et al.* (1991a,b) study are presented in Tables 5 and 6, respectively.

After comparing the two methods of model fitting, the second was judged to provide a better description of the dose response relationship in the range of the TD_{05}. These fits were used to generate the final TD_{05}s. Plots of the collapsed data and the final fitted models are displayed in Figure 2. The TD_{05}s and model-fitting information are presented in Table 7. For female rats, values for the TD_{05} (95% lower confidence limit, or LCL) range from 34 µg/kg-bw per day (95% LCL = 18 µg/kg-bw per day) for hepatic biliary cystadenoma to 82 µg/kg-bw per day (95% LCL = 61 µg/kg-bw per day) for hepatic carcinoma. For male rats, values for the TD_{05} (95% LCL) range from 35 µg/kg-bw per day (95% LCL = 29 µg/kg-bw per day) for hepatic biliary cystadenoma to 78 µg/kg-bw per day (95% LCL = 48 µg/kg-bw per day) for hepatic hemangiosarcoma.

TABLE 5 Data on hepatic carcinogenicity in male rats used for modelling

Carcinoma		Hemangiosarcoma		Biliary cystadenoma	
Intake (mg/kg-bw per day)	**Incidence**	**Intake (mg/kg-bw per day)**	**Incidence**	**Intake (mg/kg-bw per day)**	**Incidence**
0	2/192	0	2/192	0	2/192
0.0020	2/96	0.002	0/96	0.0020	4/96
0.0080	3/96	0.005	1/48	0.0080	4/96
0.0330	4/96	0.011	2/48	0.0330	2/96
0.0760	11/96	0.022	0/48	0.0760	10/96
0.1200	26/96	0.044	1/48	0.1200	24/96
0.1960	44/96	0.065	1/48	0.1960	26/96
0.3045	66/96	0.087	6/48	0.3045	33/96
		0.109	6/48		
		0.131	14/48		

TABLE 6 Data on hepatic carcinogenicity in female rats used for modelling

Carcinoma		Biliary cystadenoma	
Intake (mg/kg-bw per day)	**Incidence**	**Intake (mg/kg-bw per day)**	**Incidence**
0	2/192	0	4/192
0.0035	0/96	0.002	1/48
0.0145	4/96	0.005	4/48
0.057	8/96	0.010	0/48
0.134	10/96	0.019	3/48
0.210	10/96	0.038	5/48
0.344	19/96	0.076	7/48
0.459	18/48	0.115	34/48
0.612	33/48		

FIGURE 2 TD_{05}s for NDMA

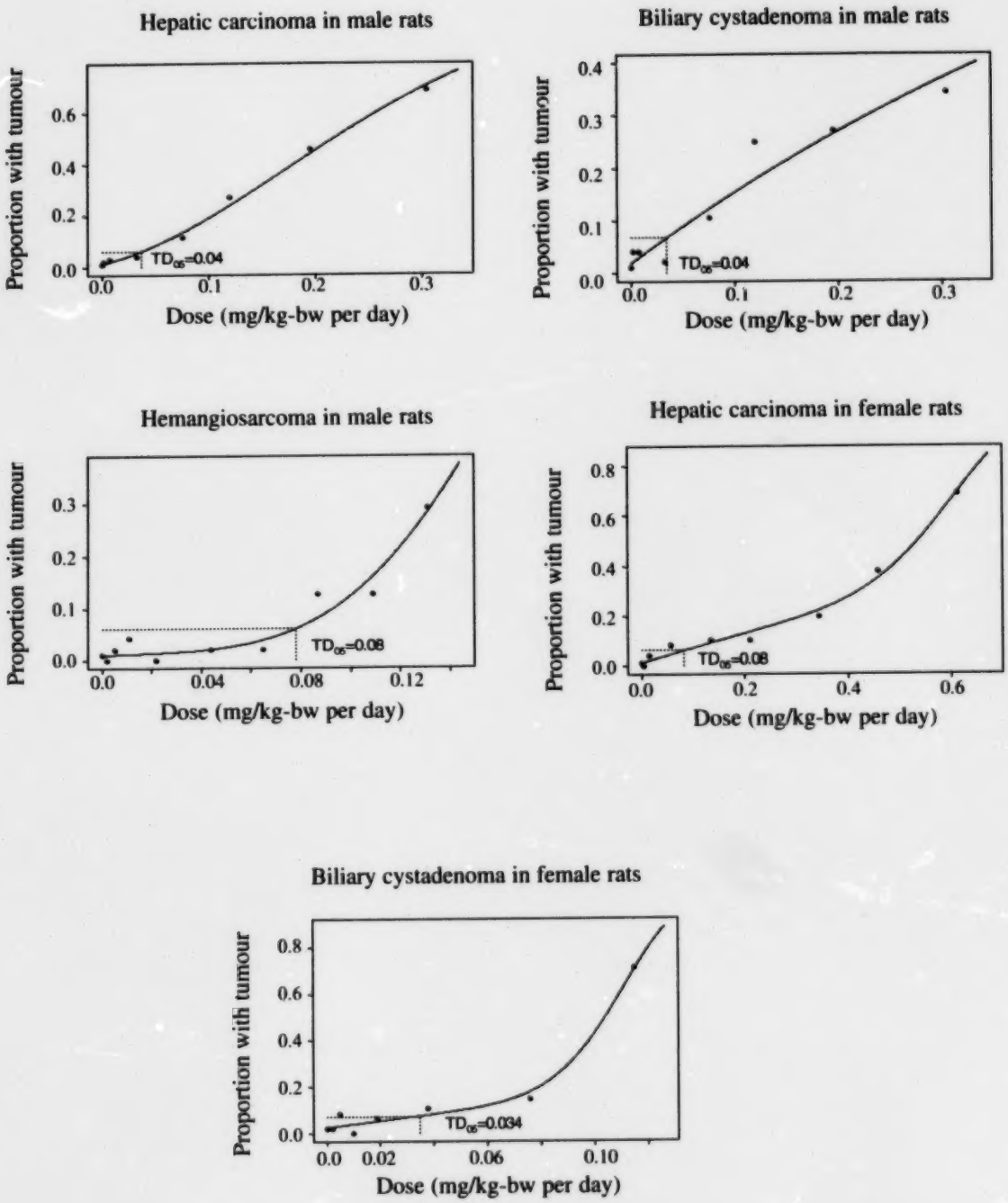

TABLE 7 TD_{05}s for NDMA

	TD_{05} (μg/kg-bw per day)	95% LCL on TD_{05}	Chi-square	df	p-value
Male rats					
Hepatic carcinoma	38	24	2.17	5	0.82
Hepatic hemangiosarcoma	78	48	7.67	6	0.26
Hepatic biliary cystadenoma	35	29	10.25	6	0.11
Female rats					
Hepatic carcinoma	82	61	7.36	5	0.19
Hepatic biliary cystadenoma	34	18	7.036	5	0.22

Based upon extensive analysis of the results of this bioassay, Peto *et al.* (1984) derived the following relationship between cumulative liver tumour incidence in the female Colworth-Wistar rats, exposure time and dose:

$$CI = 51.45(d + 0.1)^6 \times t^7$$

where CI is the cumulative incidence, d is the dose in mg/kg-bw per day and t is the exposure time in years. For males, the relationship between cumulative liver tumour incidence, exposure time and dose was:

$$CI = 37.43(d + 0.1)^6 \times t^7$$

where the terms are as defined above.

3.3.3.2 Non-neoplastic effects

Information on non-neoplastic effects in humans associated with exposure to NDMA is inadequate to characterize exposure–response.

Effects on the liver (i.e., hepatocyte vacuolization, portal venopathy and necrosis/hemorrhage) and kidney (i.e., glomerulus dilatation and slight thickening of the Bowman's capsule), "congestion" in the spleen and lungs, and gastrointestinal hemorrhage have been reported in early short-term and subchronic studies of animals receiving greater than 0.2 mg NDMA/kg-bw per day. Embryo toxicity and embryo lethality have been observed in a number of early, inadequately reported studies following oral exposure to high (maternally toxic) doses in the range of 20–30 mg/kg-bw per day or lower doses upon repeated exposure (1.4–2.9 mg/kg-bw per day by gavage or 5 mg/kg-bw per day in diet); teratogenicity has not been reported. In one report of a single-generation study (Anderson *et al.*, 1978) in mice, the number of stillbirths and neonatal deaths (combined) was increased 2-fold at 0.1 mg/L (estimated daily intake of 0.02 mg NDMA/kg-bw per day). However, confidence in the significance of this observation is mitigated by the lack of a more reliable estimate of intake, the absence of significant effects on other reproductive parameters, the lack of histopathological changes to account for the increased mortality, as well as the observation of no increased fetal mortality in dams administered a higher total dose of NDMA (Anderson *et al.*, 1989).

Although suppression of cell- and humoral-mediated immune responses was reported in mice consuming doses greater than approximately 0.05 μg/kg-bw per day in drinking water for 30–120 days, effects were fully reversible within 30 days of cessation of exposure.

Based on available documented studies, therefore, non-neoplastic effects of NDMA have rarely been consistently observed; where they

have been observed, they have typically occurred (except for one report of the single-generation reproduction study) at doses greater than those at which increases in tumour incidence have been reported in other studies (i.e., the latter was observed at doses as low as about 0.1 mg/kg-bw per day in rats). In addition, in view of the likely critical role of the genotoxicity of NDMA, for which the weight of evidence is consistent and convincing in the induction of tumours, cancer is clearly the critical endpoint for quantitation of exposure–response for risk characterization, and measures based on this endpoint will be protective for other reported non-neoplastic effects.

3.3.4 Human health risk characterization

It should be noted that, with the exception of monitoring of NDMA in water supplies in Ontario, most of the sampling and analyses for this contaminant in the general environment have been source directed — i.e., confined to foodstuffs in which it is most likely to be present or media in the vicinity of industrial sources.[3] Moreover, while estimates of intake in food are presented primarily as a basis for comparison with those from other media, the early data on which these estimates are based may not be representative of the situation today, due to the impact of subsequent introduction of changes in food processing and controls to limit the formation of NDMA in food. While notifications of cosmetics with levels of nitrosamines exceeding 10 µg/kg are precluded in Canada, with the exception of baby bottle nipples and pacifiers for which the maximum content is specified under the *Hazardous Products Act* and Regulations, the NDMA content of other rubber-containing products in Canada is largely unknown. Owing primarily to limitations of the available data, therefore, the principal focus of the human health risk characterization is media contaminated in the vicinity of industrial point sources, for which available data are those collected at several locations in Ontario in the early 1990s.

For substances such as NDMA, for which it is likely that the mode of action for the induction of tumours involves direct interaction with genetic material, estimates of exposure are compared with quantitative estimates of carcinogenic potency (Exposure Potency Index, or EPI) to characterize risk and to provide guidance in establishing priorities for further action (i.e., analysis of options to reduce exposure) under CEPA 1999. Calculated values of the TD_{05} for the development of hepatic tumours in male and female rats exposed to NDMA in the critical study (Brantom, 1983; Peto *et al.*, 1991a,b) were similar. The lowest TD_{05} was 34 µg/kg-bw per day for the development of biliary cystadenomas in female animals; the 95% LCL was 18 µg/kg-bw per day (Table 7). The margins between carcinogenic potency and estimated intakes of NDMA, based upon the levels of this substance detected in ambient air and contaminated drinking water (groundwater), both in the vicinity of point sources and in drinking water surveyed across the province of Ontario, are presented in the table below. On the basis of this (possibly unrepresentative) information from short-term monitoring surveys of ambient air (and contaminated drinking water) near industrial facilities, the priority for investigation of options to reduce exposure to NDMA in the vicinity of such point sources is considered to be high.

[3] NDMA was not detected in a single survey of ambient air not impacted by point sources.

Estimated daily intake of NDMA	TD_{05} (95% LCL) (μg/kg-bw per day)	Margin between potency and estimated intake	Exposure Potency Index (EPI)	Priority for further action (Health Canada, 1994)
0.011 μg/kg-bw per day: highest worst-case estimate of daily intake of NDMA based upon censored mean concentrations in ambient air in close proximity to point sources (Table 4)	34 (18)	3100 (1600)	3.2×10^{-4} (6.3×10^{-4})	High (High)
Drinking water in Ontario (Table 4):				
0.0013 μg/kg-bw per day: highest estimated daily intake of NDMA, based upon mean level	34 (18)	26 200 (13 800)	3.8×10^{-5} (7.3×10^{-5})	Moderate (Moderate)
0.004 μg/kg-bw per day: highest estimated daily intake of NDMA, based upon the maximum level measured	34 (18)	8500 (4500)	1.2×10^{-4} (2.2×10^{-4})	Moderate (High)
Contaminated drinking water (i.e., well water in the vicinity of an industrial facility in Canada) (Table 4):				
0.14 μg/kg-bw per day: highest worst-case estimate of daily intake of NDMA, based upon minimum level measured	34 (18)	240 (130)	4.2×10^{-3} (7.7×10^{-3})	High (High)
0.31 μg/kg-bw per day: highest worst-case estimate of daily intake of NDMA, based upon maximum level measured	34 (18)	100 (60)	1.0×10^{-2} (1.7×10^{-2})	High (High)

3.3.5 *Uncertainties and degree of confidence in human health risk characterization*

There is a high degree of uncertainty in the quantitative estimates of intake of NDMA. Except for situations of direct industrial discharge to the atmosphere, concentrations of NDMA in outdoor air are typically below limits of detection, despite the sensitive methodologies available for its detection. Cases where NDMA has been detected in outdoor air in the vicinity of industrial point sources have been restricted to a few sites in southern Ontario, where measured concentrations have been highly variable and largely dependent on the proximity of the sampling site to the point source and on the wind direction. Additional uncertainty is introduced by the conservative assumption that the average and maximum concentrations from short-term measurements are

similar to 24-hour average concentrations at these locations. In reality, concentrations are likely to be at least an order of magnitude lower for these longer averaging times. As the proportion of the general population directly impacted by industrial atmospheric emissions containing NDMA is unknown, but likely to be small, there is considerable uncertainty concerning the relevance of the reasonable worst-case estimates of intake by inhalation to the general population as a whole.

There is a high degree of uncertainty concerning the concentrations of NDMA in the indoor air of residences and public places in Canada, as no relevant data were identified. In other countries, ETS has contributed to elevated levels of NDMA in the indoor air of public places where smoking is permitted, but no data are available concerning concentrations in residential locations. Nevertheless, there is a reasonably high degree of certainty that daily exposure to ETS would result in intakes of NDMA in Canada that are 1 or 2 orders of magnitude higher than intakes from any other route or exposure pathway. Although data concerning the NDMA content of mainstream smoke from Canadian cigarettes were not identified, there is a high degree of certainty that the daily intake of NDMA by smokers is greater than intakes by non-smokers.

There is a moderate degree of uncertainty concerning the concentrations of NDMA in the drinking water consumed in Canada. Data are available only for the province of Ontario, where concentrations of NDMA are generally below the limits of detection of the sensitive methodologies employed. The formation of NDMA in drinking water from a small number of water treatment plants in Ontario resulted in extensive efforts to identify the cause and minimize this formation. There is no information available concerning similar potential in other provinces. Considerably higher concentrations of NDMA were measured in supply wells at a single location in southern Ontario, as a consequence of contamination of groundwater by a nearby industrial facility. Although this may be an isolated incident, as no information was identified concerning contamination of groundwater destined for human consumption elsewhere in Canada, it does indicate potential (at least in the past) for contamination of groundwater sources in the vicinity of industrial point sources.

There is a moderate degree of uncertainty concerning intake from ingestion of foods in which NDMA is formed during processing, preservation and/or preparation. Following the identification of NDMA in foods, relatively intensive international monitoring efforts led to a focus on a relatively small number of food categories for which remedial methods have been largely successful in minimizing formation of NDMA. While there is a general consensus that concentrations of NDMA in foods in developed countries are currently less than historic levels, representative data concerning recent or current concentrations of NDMA in foods in Canada were not identified. Uncertainty is introduced by the assumption that historic maximum concentrations can be used to develop reasonable worst-case estimates of current intake of NDMA by ingestion. Additional uncertainty is introduced by the assumption that the concentration of NDMA is zero in the large number of food items for which no data concerning concentrations of NDMA are available. However, this assumption is not unreasonable, since most of these foods are unlikely to contain both precursor amines and nitrosating agents.

Although historic maximum concentrations of NDMA in foods in Canada were the basis of the reasonable worst-case estimates of intake, average per capita daily rates of consumption of these food items were assumed. It is certain that individuals within the general population consume favourite foods or beverages at rates far greater than these average per capita daily rates. For example, the per capita average daily intake rate of beer for adults (i.e., 20–59 years) is 111 mL/day (EHD, 1998), but an adult consuming several beers on a daily basis would consume perhaps 1 L/day — the corresponding intake of NDMA from beer would be 10 times higher.

There is a reasonable degree of certainty that exposure of the general population to NDMA in personal care products is minimal, since nitrosamine content of greater than 10 µg/kg in cosmetics in Canada is precluded, upon notification. However, some uncertainty exists, since there is no evidence of systematic monitoring programs to ensure regulatory compliance.

Non-neoplastic effects associated with exposure to NDMA have not been well studied. Although non-neoplastic effects in laboratory animals have typically been observed only at dose levels higher than those associated with increased tumour incidence (approximately 0.1 mg/kg-bw per day in rats), in one report, stillborn and neonatal deaths (combined) were observed in a single-generation study in mice receiving an estimated intake of approximately 0.02 mg/kg-bw per day for 75 days. While there is uncertainty surrounding the biological significance of this finding, further experimental work in this area would provide more definitive information concerning potential reproductive effects linked to long-term exposure to low levels of NDMA.

There is a high degree of certainty that the genotoxicity of NDMA (likely involving the formation of *O*⁶-methylguanine in DNA) is critical in the mechanism of carcinogenicity of this substance. Also, due to the unusually large number of dose groups in the critical study, characterization of exposure–response for induction of tumours by NDMA in laboratory animals is considered to be optimal. Based upon the highest TD_{05} identified from the study in which exposure–response was best characterized (i.e., 82 µg/kg-bw per day for hepatic carcinomas in female rats), the resulting EPIs would be approximately 2.5-fold lower than those derived (in Section 3.3.4) on the basis of the hepatic biliary cystadenomas in female rats. The 95% LCL on the lowest TD_{05} on which the EPIs were based was 18 µg/kg-bw per day versus the maximum likelihood estimate of 34 µg/kg-bw per day.

3.4 Conclusions

CEPA 1999 64(a): Based on available data, NDMA is not entering the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity. Therefore, NDMA is not considered to be "toxic" as defined under Paragraph 64(a) of CEPA 1999.

CEPA 1999 64(b): Based on available data, NDMA is not entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger to the environment on which life depends. Therefore, NDMA is not considered to be "toxic" as defined under Paragraph 64(b) of CEPA 1999.

CEPA 1999 64(c): Based on available data, it has been concluded that NDMA is entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health. Therefore, NDMA is considered to be "toxic" as defined under Paragraph 64(c) of CEPA 1999. This approach is consistent with the objective that exposure to substances where cancer is likely induced through direct interaction with genetic material be reduced wherever possible and obviates the need to establish an arbitrary "*de minimis*" level of risk for the determination of "toxic" under CEPA 1999. On

the basis of worst-case estimates, priority for investigation of options to reduce exposure from NDMA in ambient air in the vicinity of point sources is considered to be high.

Overall conclusion: Based on critical assessment of relevant information, NDMA is considered to be "toxic" as defined in Section 64 of CEPA 1999.

3.5 Considerations for follow-up (further action)

There have been a number of measures taken to limit exposure of the general population in Canada to NDMA. Since 1975, the potential for formation in foodstuffs has been reduced through changes in food processing, some of which have been mandated under the *Canadian Food and Drugs Act* and Regulations. Notifications of cosmetics with levels of nitrosamines exceeding 10 µg/kg are precluded, and, under the *Hazardous Products Act* and Regulations, infant feeding bottle nipples and pacifiers may not contain more than 10 mg total volatile N-nitrosamines/kg.

While several steps have been taken to reduce exposure of the general population in Canada, recent data on the NDMA content of foodstuffs and rubber-containing products in Canada other than infant feeding bottle nipples and pacifiers have not been identified. Moreover, with the exception of monitoring conducted in Ontario in the early 1990s, potential for exposure to NDMA in the vincinity of point sources in Canada is also largely unknown, although stakeholders under the voluntary ARET program have committed to reducing total emissions of NDMA from 6000 g in 1993 to 87 g by the year 2000 (ARET Secretariat, 1998).

Continued monitoring of levels of nitrosamines (including NDMA) in Canadian foodstuffs to verify reduction of content seems warranted. Determination of the potential presence of nitrosamines (including NDMA) in rubber products other than infant feeding bottle nipples and pacifiers may also be warranted, particularly for those products with which infants (who exhibit mouthing behaviour) come into contact.

On the basis of limited information from short-term monitoring surveys of ambient air and water near industrial facilities, the priority for investigation of options to reduce exposure to NDMA in the vicinity of such point sources is considered high. It is recommended, therefore, that there be additional investigation of the magnitude of exposure of populations in the vicinity of point sources to assist risk management actions.

Optimization of drinking water treatment to minimize formation of NDMA is also recommended, though such measures must not compromise human health protection.

Since NDMA may be released directly to the environment through the application of certain pesticides, the levels of this nitrosamine in products regulated under the *Pest Control Products Act* should also continue to be monitored. As indicated in Section 2.2.2.2, monitoring by the Pest Management Regulatory Agency has shown that the review standard of 1 µg/g is rarely exceeded.

Owing to the common practice in Canada of applying sewage sludge to agricultural lands and the potential for uptake by plants, it is recommended that concentrations of NDMA in such sludge be monitored to determine the potential of this practice to contribute to the exposure of humans and non-human organisms.

Since NDMA is likely to be carcinogenic to humans at relatively low levels of exposure and is not currently used in commerce in Canada, it is recommended that the manufacture, import and use of the substance be banned in order to prevent its introduction into the Canadian market.

4.0 REFERENCES

Abanobi, S.E., E. Farber and D.S.R. Sarma. 1979. Persistence of DNA damage during development of liver angiosarcoma in rats fed dimethylnitrosamine. Cancer Res. 39: 1592–1596.

Adams, J.D., K.J. O'Mara-Adams and D. Hoffmann. 1987. Toxic and carcinogenic agents in undiluted mainstream smoke and sidestream smoke of different types of cigarettes. Carcinogenesis 8(5): 729–731.

Agrelo, C., J.C. Phillips, B.G. Lake, R.C. Longland and S.D. Gangolli. 1978. Studies on the gastrointestinal absorption of *N*-nitrosamines: effect of dietary constituents. Toxicology 10: 159–167.

Alexandrov, V.A. 1968. Blastomogenic effect of dimethylnitrosamine on pregnant rats and their offspring. Nature 218: 280–281.

Alexandrov, V.A. 1974. [Embryotoxic and transplacental oncogenic action of symmetrical dialkylnitrosamines on the progeny of rats.] Bull. Exp. Biol. Med. 78: 1308–1310 (in Russian) [cited in ATSDR, 1989].

Althoff, J., P. Pour, C. Grandjean and S. Marsh. 1977. Transplacental effects of nitrosamines in Syrian hamsters. Z. Krebsforsch. 90: 79–86.

Anderson, L.M. 1988. Increased numbers of *N*-nitrosodimethylamine-initiated lung tumours in mice by chronic co-administration of ethanol. Carcinogenesis 9: 1717–1719.

Anderson, L.M. 1992. Modulation of nitrosamine metabolism by ethanol: implications for cancer risk. *In*: R.R. Watson (ed.), Alcohol and cancer. CRC Press, Boca Raton, Florida. pp. 17–54.

Anderson, L.M., A. Giner-Sorolla, D. Ebeling and J.M. Budinger. 1978. Effects of imipramine, nitrite, and dimethylnitrosamine on reproduction in mice. Res. Commun. Chem. Pathol. Pharmacol. 19: 311–327.

Anderson, L.M., L.J. Priest and J.M. Budinger. 1979. Lung tumorigenesis in mice after chronic exposure in early life to a low dose of dimethylnitrosamine. J. Natl. Cancer Inst. 62: 1553–1555.

Anderson, L.M., G.W. Harrington, H.M. Pylypiw, Jr., A. Hagiwara and P.N. Magee. 1986. Tissue levels and biological effects of *N*-nitrosodimethylamine in mice during chronic low or high dose exposure with or without ethanol. Drug Metab. Dispos. 14(6): 733–739.

Anderson, L.M., A. Hagiwara, R.M. Kovatch, S. Rehm and J.M. Rice. 1989. Transplacental initiation of liver, lung, neurogenic, and connective tissue tumors by *N*-nitroso compounds in mice. Fundam. Appl. Toxicol. 12: 604–620.

Anderson, L.M., R. Koseniauskas, E.S. Burak, T.J. Moskal, C.T. Gombar, J.M. Phillips, E.B. Sansone, S. Keimig, P.N. Magee, J.M. Rice and G.W. Harrington. 1992a. Reduced blood clearance and increased urinary excretion of *N*-nitrosodimethylamine in patas monkeys exposed to ethanol or isopropyl alcohol. Cancer Res. 52: 1463–1468.

Anderson, L.M., J.P. Carter, D.L. Logsdon, C.L. Driver and R.M. Kovatch. 1992b. Characterization of ethanol's enhancement of tumorigenesis by *N*-nitrosodimethylamine in mice. Carcinogenesis 13: 2107–2111.

Anderson, L.M., R. Koseniauskas, E.S. Burak, D.L. Logsdon, J.P. Carter, C.L. Driver, C.T. Gombar, P.N. Magee and G.W. Harrington. 1994. Suppression of *in vivo* clearance of *N*-nitrosodimethylamine in mice by cotreatment with ethanol. Drug Metab. Dispos. 22: 43–49.

Anderson, L.M., S.K. Chhabra, P.V. Nerurkar, V.L. Souliotis and S.A. Kyrtopoulos. 1995. Alcohol-related cancer risk: a toxicokinetic hypothesis. Alcohol 12: 97–104.

Anderson, L.M., V.L. Souliotis, S.K. Chhabra, T.J. Moskal, S.D. Harbaugh and S.A. Kyrtopoulos. 1996. *N*-Nitrosodimethylamine-derived O^6-methylguanine in DNA of monkey gastrointestinal and urogenital organs and enhancement by ethanol. Int. J. Cancer 66: 130–134.

Arai, M., Y. Aoki, K. Nakanishi, Y. Miyata, T. Mori and N. Ito. 1979. Long-term experiment of maximal non-carcinogenic dose of dimethylnitrosamine for carcinogenesis in rats. Gann 70: 549–558.

ARET (Accelerated Reduction/Elimination of Toxics) Secretariat. 1998. Environmental Leaders 2: ARET voluntary action on toxic substances. Update. Ottawa, Ontario. 49 pp.

Asakura, S., S. Sawada, H. Daimon, T. Fukuda, K. Ogura, K. Yamatsu and C. Furihata. 1994. Effects of dietary restriction on induction of unscheduled DNA synthesis (UDS) and replicative DNA synthesis (RDS) in rat liver. Mutat. Res. 322: 257–264.

Atkinson, R. 1985. Kinetics and mechanisms of the gas-phase reactions of hydroxyl radicals with organic compounds under atmospheric conditions. Chem. Rev. 85: 69–201.

ATSDR (Agency for Toxic Substances and Disease Registry). 1989. Toxicological profile for *N*-nitrosodimethylamine. Prepared by the Syracuse Research Corporation for ATSDR in collaboration with the U.S. Environmental Protection Agency. U.S. Public Health Service, Washington, D.C. 119 pp.

Ayanaba, A. and M. Alexander. 1974. Transformation of methylamines and formation of a hazardous product, dimethylnitrosamine, in samples of treated sewage and lake water. J. Environ. Qual. 3: 83–89.

Ballantine, J. 1997. Personal communication (letter dated September 24, 1997). Regulatory Affairs and Innovations Division, Pest Management Regulatory Agency, Health Canada.

Barbin, A., J.-C. Béréziat and H. Bartsch. 1983. Evaluation of DNA damage by the alkaline elution technique in liver, kidneys and lungs of rats and hamsters treated with *N*-nitroso-dialkylamines. Carcinogenesis 4: 541–545.

Barcelo, S., J.M. Gerdiner, A. Gescher and J.K Chipman. 1996. CYP2E1-mediated mechanism of anti-genotoxicity of the broccoli constituent sulforaphane. Carcinogenesis 17: 277–282.

Barnes, J.M. and P.N. Magee. 1954. Some toxic properties of dimethylnitrosamine. Br. J. Ind. Med. 11: 167–174 [cited in ATSDR, 1989].

Bauknecht, Th., W. Vogel, U. Bayer and D. Wild. 1977. Comparative *in vivo* mutagenicity testing by SCE and micronucleus induction in mouse bone marrow. Hum. Genet. 35: 299–307.

Bermudez, E., J.C. Mirsalis and H.C. Eales. 1982. Detection of DNA damage in primary cultures of rat hepatocytes following *in vivo* and *in vitro* exposure to genotoxic agents. Environ. Mutagen. 4: 667–679.

Bhattacharyya, K. 1965. Fetal and neonatal responses to hepatotoxic agents. J. Pathol. Bacteriol. 90: 151–161 [cited in ATSDR, 1989].

Biaudet, H., L. Mouillet and G. Debry. 1997. Migration of nitrosamines from condoms to physiological secretions. Bull. Environ. Contam. Toxicol. 59: 847–853.

BIBRA Toxicology International. 1997. *N*-Nitrosodimethylamine (NDMA). Report prepared for Health Canada. Carshalton, Surrey, U.K.

BIBRA Toxicology International. 1998. Endogenous formation of *N*-nitrosamines. Report prepared for Health Canada. Carshalton, Surrey, U.K.

Bolognesi, C., L. Rossi and L. Santi. 1988. A new method to reveal the genotoxic effects of *N*-nitrosodimethylamine in pregnant mice. Mutat. Res. 207: 57–62.

Braithwaite, I. and J. Ashby. 1988. A non-invasive micronucleus assay in the rat liver. Mutat. Res. 203: 23–32.

Brambilla, G., M. Cavanna, A. Pino and L. Robbiano. 1981. Quantitative correlation among DNA damaging potency of six *N*-nitroso compounds and their potency in inducing tumor growth and bacterial mutations. Carcinogenesis 2: 425–429.

Brambilla, G., P. Carlo, R. Finollo and L. Sciabà. 1987. Dose–response curves for liver DNA fragmentation induced in rats by sixteen *N*-nitroso compounds as measured by viscometric and alkaline elution analyses. Cancer Res. 47: 3485–3491.

Brantom, P.G. 1983. Dose–response relationships in nitrosamine carcinogenesis. Ph.D. thesis, University of Surrey, Guildford, U.K. British Industrial Biological Research Association (BIBRA), Carshalton, Surrey, U.K. 158 pp.

Brendler, S.Y., A. Tompa, K.F. Hutter, R. Preussmann and B.L. Pool-Zobel. 1992. *In vivo* and *in vitro* genotoxicity of several *N*-nitrosamines in extrahepatic tissues of the rat. Carcinogenesis 13: 2435–2441.

Brunnemann, K.D. and D. Hoffmann. 1978. Analysis of volatile nitrosamines in tobacco smoke and polluted indoor environments. Chemical studies on tobacco smoke LIX. IARC Sci. Publ. 19: 343–356.

Budavari, S., M.J. O'Neil, A.S. Smith and P.E. Heckelman. 1989. The Merck Index — An encyclopedia of chemicals, drugs, and biologicals. 11th edition. Merck & Company, Inc., Rahway, New Jersey. 1606 pp.

Bunce, N. 1996. Atmospheric properties of substances on the Priority Substances List #2 (PSL2). Contract report prepared for Environment Canada, Ottawa, Ontario. University of Guelph, Guelph, Ontario. 13 pp.

Butterworth, B.E., M.V. Templin, A.A. Constan, C.S. Sprankle, B.A. Wong, L.J. Pluta, J.I. Everitt and L. Recio. 1998. Long-term mutagenicity studies with chloroform and dimethylnitrosamine in female *lac I* transgenic B6C3F1 mice. Environ. Mol. Mutagen. 31: 248–256.

Bysshe, S.E. 1982. Bioconcentration factor in aquatic organisms. *In*: W.J. Lyman, W.F. Reehl and D.H. Rosenblatt (eds.), Handbook of chemical property estimation methods. American Chemical Society, Washington, D.C. pp. 5–6.

Callahan, M.A., M.W. Slimak, N.W. Gabel, I.P. May, C.F. Fowler, J.R. Freed, P. Jennings, R.L. Durfee, F.C. Whitemore, B. Maestri, W.R. Mabey, B.R. Holt and C. Gould. 1979. Water related environmental fate of 129 priority pollutants. Versar, Inc., Springfield, Virginia (EPA-440-4-79-029a,b).

Camus, A.-M., J.-C. Béréziat, D.E.G. Shuker, E. Hietanen, C.P. Wild, R. Montesano and H. Bartsch. 1990. Effects of a high fat diet on liver DNA methylation in rats exposed to *N*-nitrosodimethylamine. Carcinogenesis 11: 2093–2095.

CARB (California Air Resources Board). 1994. Toxic volatile organic compounds in environmental tobacco smoke: Emission factors for modeling exposures of California populations. Prepared by J.M. Daisey, K.R.R. Mahanam and A.T. Hodgson, Lawrence Berkeley Laboratory, University of California, Berkeley, California. Prepared for CARB, California Environmental Protection Agency, Sacramento, California (Final Report Contract No. A133-186).

Carter, R.L., W.H. Percival and F.J.C. Roe. 1969. Exceptional sensitivity of mink to the hepatotoxic effects of dimethylnitrosamine. J. Pathol. 97: 79–88 [cited in ATSDR, 1989].

Cesarone, C.F., C. Bolognesi and L. Santi. 1979. DNA repair synthesis in mice spermatids after treatment with *N*-methyl-*N*-nitroso-urea and *N*,*N*-dimethylnitrosamine: preliminary results. Toxicology 12: 183–186.

Cesarone, C.F., C. Bolognesi and L. Santi. 1982. Evaluation of damage to DNA after *in vivo* exposure to different classes of chemicals. Arch. Toxicol., Suppl. 5: 355–359.

Chhabra, S.K., V.L. Souliotis, A.B. Jones, L.M. Anderson and S.A. Kyrotopoulos. 1995. *O*-Methylguanine DNA-adduct formation and modulation by ethanol in placenta and fetal tissues after exposure of pregnant patas monkeys to *N*-nitrosodimethylamine. Proc. Am. Cancer Assoc. 36: 150.

Clapp, N.K. and R.E. Toya. 1970. Effect of cumulative dose and dose rate on dimethyl-nitrosamine oncogenesis in RF mice. J. Natl. Cancer Inst. 45: 495–498.

Clayton, G. and F. Clayton (eds.). 1981. Patty's industrial hygiene and toxicology. 3rd edition. John Wiley and Sons, New York, N.Y. pp. 2786–2788.

Cliet, I., E. Fournier, C. Melcion and A. Cordier. 1989. *In vivo* micronucleus test using mouse hepatocytes. Mutat. Res. 216: 321–326.

Cliet, I., C. Melcion and A. Cordier. 1993. Lack of predictivity of bone marrow micronucleus test versus testis micronucleus test: comparison with four carcinogens. Mutat. Res. 292: 105–111.

Coccia, P., M. Salmona, L. Diomede, L. Citti, L. Mariani and M. Romano. 1988. Liver DNA alkylation after a single carcinogenic dose of dimethylnitrosoamine to newborn and adult CFW Swiss mice. Chem.-Biol. Interact. 68: 259–271.

Cohen, J.B. and J.D. Bachman. 1978. Measurement of environmental nitrosamines. IARC Sci. Publ. 19: 357–372.

Cooper, S.F., C. Lemoyne and D. Gauvreau. 1987. Identification and quantitation of *N*-nitrosamines in human postmortem organs. J. Anal. Toxicol. 11: 12–18.

Cornée, J., D. Lairon, J. Velema, M. Guyader and P. Berthezene. 1992. An estimate of nitrate, nitrite and *N*-nitrosodimethyl-amine concentrations in French food products or food groups. Sci. Aliments 12: 155–197.

CRA (Conestoga-Rovers & Associates). 1994. Treatability test report for Conestoga-Rovers & Associates on Rayox UV/oxidation treatment of Uniroyal off-site groundwater. Waterloo, Ontario. December.

CSGMT (Collaborative Study Group for the Micronucleus Test). 1986. Sex difference in the micronucleus test. Mutat. Res. 172: 151–163.

Daugherty, J.P. and N.K. Clapp. 1976. Studies on nitrosamine metabolism: I. Subcellular distribution of radioactivity in tumor-susceptible tissues of RFM mice following administration of (^{14}C)dimethylnitrosamine. Life Sci. 19: 265–271 [cited in ATSDR, 1989].

Dean-Raymond, D. and M. Alexander. 1976. Plant uptake and leaching of dimethylnitrosamine. Nature 262: 394.

Desjardins, R., M. Fournier, F. Denizeau and K. Krzystyniak. 1992. Immunosuppression by chronic exposure to *N*-nitrosodimethylamine (NDMA) in mice. J. Toxicol. Environ. Health 37: 351–361.

De Stefani, E., H. Deneo-Pellegrini, J.C. Carzoglio, A. Ronco and M. Mendilaharsu. 1996. Dietary nitrosodimethylamine and the risk of lung cancer: a case–control study from Uruguay. Cancer Epidemiol. Biomarkers Prev. 5: 679–682.

Devereux, T.R., M.W. Anderson and S.A. Belinsky. 1991. Role of *ras* protooncogene activation in the formation of spontaneous and nitrosamine-induced lung tumours in the resistant C3H mouse. Carcinogenesis 12: 299–303.

Diaz Gomez, M.I., P.F. Swann and P.N. Magee. 1977. The absorption and metabolism in rats of small oral doses of dimethylnitrosamine. Biochem. J. 164: 497–500.

Diaz Gomez, M.I., D. Tamayo and J.A. Castro. 1986. Administration of *N*-nitrosodimethylamine, *N*-nitrosopyrrolidine, or *N'*-nitrosonornicotine to nursing rats: their interactions with liver and kidney nucleic acids from sucklings. J. Natl. Cancer Inst. 76(6): 1133–1136.

DMER (Don Mackay Environmental Research) and AEL (Angus Environmental Limited). 1996. Pathways analysis using fugacity modelling of *N*-nitrosodimethylamine for the second Priority Substances List. Unpublished report prepared for the Chemicals Evaluation Division, Commercial Chemicals Evaluation Branch, Environment Canada, Hull, Quebec. DMER, Peterborough, Ontario, and AEL, Don Mills, Ontario. 63 pp.

Doolittle, D.J., E. Bermudez, P.K. Working and B.E. Butterworth. 1984. Measurement of genotoxic activity in multiple tissues following inhalation exposure to dimethylnitrosamine. Mutat. Res. 141: 123–127.

Draper, A.C. and W.S. Brewer. 1979. Measurement of the aquatic toxicity of volatile nitrosamines. J. Toxicol. Environ. Health 5: 985–993.

Draper, A.C. and J.W. Fisher. 1980. The effects of selected aquatic sediments on the acute toxicity of *N*-nitrosodimethylamine to *Gammarus limnaeus*. Aerospace Medical Research Laboratory, Wright-Patterson Air Force Base, Ohio. 10 pp. (Technical Report No. AMBL-TR-79-94).

Dunn, S.R., J.W. Pensabene and M.L. Simenhoff. 1986. Analysis of human blood for volatile *N*-nitrosamines by gas chromatography–chemiluminescence detection. J. Chromatogr. 377: 35–47.

ECETOC (European Chemical Industry Ecology & Toxicology Centre). 1990. Human exposure to *N*-nitrosamines, their effects, and a risk assessment for *N*-nitrosodiethanolamine in personal care products. European Centre for Ecotoxicology and Toxicology of Chemicals, Brussels, Belgium (Technical Report No. 41; ISSN-07773-8072-41).

ECETOC (European Chemical Industry Ecology & Toxicology Centre). 1991. Critical evaluation of methods for the determination

of *N*-nitrosamines in personal care and household products. European Centre for Ecotoxicology and Toxicology of Chemicals, Brussels, Belgium (Technical Report No. 42; ISSN-0773-8072-42).

ECETOC (European Chemical Industry Ecology & Toxicology Centre). 1994. Assessment of non-occupational exposure to chemicals. European Centre for Ecotoxicology and Toxicology of Chemicals, Brussels, Belgium (Technical Report No. 58; ISSN-0773-8072-58).

ECO LOGIC. 1989. Special report to Regional Municipality of Waterloo. Contamination of Elmira drinking water with *N,N*-dimethylnitrosamine. Prepared by P.J. Kornelsen, D.J. Hallett and R.W. Brecher. Rockwood, Ontario. December 14, 1989.

EHD (Environmental Health Directorate). 1998. Exposure factors for assessing total daily intake of Priority Substances by the general population of Canada. Draft internal report. Bureau of Chemical Hazards, Health Canada, Ottawa, Ontario, December 18, 1998.

Encell, L., P.G. Foiles and B. Gold. 1996. The relationship between *N*-nitrosodimethylamine metabolism and DNA methylation in isolated rat hepatocytes. Carcinogenesis 17(5): 1127–1134.

Environment Canada. 1996a. Domestic Substances List. Commercial Chemicals Evaluation Branch, Hull, Quebec.

Environment Canada. 1996b. Voluntary response to special request for information on PSL2 substances which accompanied the NPRI (National Pollutant Release Inventory) survey, 1993 reporting year. Commercial Chemicals Evaluation Branch, Hull, Quebec.

Environment Canada. 1997a. Environmental assessments of Priority Substances under the *Canadian Environmental Protection Act*. Guidance manual version 1.0 — March 1997. Environmental Protection Series. Chemicals Evaluation Division, Commercial Chemicals Evaluation Branch, Hull, Quebec (EPS/2/CC/3E).

Environment Canada. 1997b. Results of the CEPA Section 16 Notice respecting the second Priority Substances List and di(2-ethylhexyl)phthalate. Use Patterns Section, Commercial Chemicals Evaluation Branch, Hull, Quebec.

Environment Canada. 1997c. Notice respecting the second Priority Substances List and di(2-ethylhexyl) phthalate. *Canada Gazette*, Part I, February 15, 1997. pp. 366–368.

Environment Canada. 1998. A joint 1997–98 DOE/provinces survey of municipal drinking water treatment facilities and distribution systems. Commercial Chemicals Evaluation Branch, Hull, Quebec.

Environment Canada and Health Canada. 2000. Notice concerning the assessment of the Priority Substance *N*-nitrosodimethylamine. *Canada Gazette*, Part I, February 5, 2000. pp. 518–521.

Espinosa-Aguirre, J.J., J. Rubio, M. Cassani, R. Nosti, S. Caballero, I. Gonzalez and G. Martinez. 1996. Induction of microsomal enzymes in liver of rats treated with cyclohexanol. Mutat. Res. 368: 103–107.

Espinosa-Aguirre, J.J., J. Rubio, I. Lopez, R. Nosti and J. Asteinza. 1997. Characterization of the CYP isozyme profile induced by cyclohexanol. Mutagenesis 12: 159–162.

Ferraro, L.A., R.E. Wolke and P.P. Yevich. 1977. Acute toxicity of water-borne dimethylnitrosamine (DMN) to *Fundulus heteroclitus* L. J. Fish. Biol. 10: 203–209.

Fiddler, W., J.W. Pensabene and W.I. Kimoto. 1985. Investigation of volatile nitrosamines in disposable protective gloves. Am. Ind. Hyg. Assoc. J. 46(8): 463–465.

Fine, D.H. and D.P. Rounbehler. 1976. Environmental *N*-nitroso compounds analysis and formation: Analysis of volatile *N*-nitroso compounds by combined gas chromatography and thermal energy analysis. IARC Sci. Publ. 14: 404–408.

Fine, D.H., D.P. Rounbehler and F. Huffman. 1975. Analysis of volatile *N*-nitroso compounds in drinking water at the part per trillion level. Bull. Environ. Contam. Toxicol. 14: 404–408.

Fine, D.H., R. Ross, D.P. Rounbehler, A. Silvergleid and L. Song. 1977. Formation *in vivo* of volatile *N*-nitrosamines in man after ingestion of cooked bacon and spinach. Nature 265: 753–755.

Freund, H.A. 1937. Clinical manifestations and studies in parenchymatous hepatitis. Ann. Intern. Med. 10: 1144–1155 [cited in ATSDR, 1989].

Fussgaenger, R.D. and H. Ditschuneit. 1980. Lethal exitus of a patient with *N*-nitroso-dimethylamine poisoning 2.5 years following the first ingestion and signs of intoxication. Oncology 37: 273–277.

Garland, W.A., H. Holowschenko, W. Kuenzig, E.P. Norkus and A.H. Conney. 1982. A high resolution mass spectrometry assay for *N*-nitrosodimethylamine in human plasma. *In*: P.N. Magee (ed.), Nitrosoamines and human cancer. Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y. pp. 183–192 (Banbury Report 12).

Goff, E.U., J.R. Coombs and D.H. Fine. 1980. Determination of *N*-nitrosamines from diesel engine crankcase emissions. Anal. Chem. 52: 1833–1836.

González, C.A., E. Riboli, J. Badosa, E. Batiste, T. Cardona, S. Pita, J.M. Sanz, M. Torrent and A. Agudo. 1994. Nutritional factors and gastric cancer in Spain. Am. J. Epidemiol. 139: 466–473.

Goodman, M.T., J.H. Hankin, L.R. Wilkens and L.N. Kolonel. 1992. High-fat foods and the risk of lung cancer. Epidemiology 3: 288–299.

Gough, T.A., K.S. Webb and P.F. Swann. 1983. An examination of human blood for the presence of volatile nitrosamines. Food Chem. Toxicol. 21(2): 151–156.

Graham, J.E., S.A. Andrews, G.J. Farquhar and O. Meresz. 1996. Factors affecting NDMA formation during drinking water treatment. Proceedings of the 1995 Water Quality Technology Conference, American Water Works Association.

Green, R. 1995. Personal communication (e-mail dated June 27, 1995). Cosmetic ingredient policy statement for nitrosamines, dated July 1993. Pharmaceutical Assessment and Cosmetics Division, Bureau of Non-Prescription Drugs, Drugs Directorate, Health Canada, Ottawa, Ontario.

Grieco, M.P., J.D. Hendricks, R.A. Scanlon, R.O. Sinnhube and D.A. Pierce. 1978. Carcinogenicity and acute toxicity of dimethylnitrosamine in rainbow trout (*Salmo gairdneri*). J. Natl. Cancer Inst. 60(5): 1127–1131.

Haggerty, H.G. and M.P. Holsapple. 1990. Role of metabolism in dimethylnitrosamine-induced immunosuppression: a review. Toxicology 63: 1–23.

Hamilton, A. and H.L. Hardy. 1974. Industrial toxicology. 3rd edition. Publishing Science Group, Inc., Acton, Massachusetts. p. 311 [cited in ATSDR, 1989].

Hanst, P.L., J.W. Spence and M. Miller. 1977. Atmospheric chemistry of *N*-nitroso dimethylamine. Environ. Sci. Technol. 11(4): 403–405.

Hard, G.C. and W.H. Butler. 1970a. Cellular analysis of renal neoplasia: light microscope study of the development of interstitial lesions induced in the rat kidney by a single carcinogenic dose of dimethylnitrosamine. Cancer Res. 30: 2806–2815.

Hard, G.C. and W.H. Butler. 1970b. Toxicity of dimethylnitrosamine for the rat testis. J. Pathol. 102: 201–207.

Hashimoto, S., T. Yokokura, Y. Kawai and M. Mutai. 1976. Dimethylnitrosamine formation in the gastro-intestinal tract of rats. Food Cosmet. Toxicol. 14: 553–556.

Havery, D.C. and H.J. Chou. 1994. Nitrosamines in sunscreens and cosmetic products. *In*: R.N. Loeppky and C.J. Michejda (eds.), Proceedings of the 204th National Meeting of the American Chemical Society on Nitrosamines and Related *N*-Nitroso Compounds, August 23–28, 1992, Washington, D.C. pp. 20–33 (ACS Symposium Series 553).

Health Canada. 1994. *Canadian Environmental Protection Act*. Human health risk assessment for Priority Substances. Minister of Supply and Services Canada, Ottawa, Ontario. 36 pp. (Catalogue No. En40-215/41E).

Health Canada. 1999. Supporting documentation (exposure) for *N*-nitrosodimethylamine. Priority Substances Section, Environmental Health Directorate, Health Canada, Ottawa, Ontario. August 1999 draft.

Herron, D.C. and R.C. Shank. 1980. Methylated purines in human liver DNA after probable dimethylnitrosamine poisoning. Cancer Res. 40: 3116–3117.

Hoffmann, D., K.D. Brunnemann, J.D. Adams and S.S. Hecht. 1984. Formation and analysis of *N*-nitrosamines in tobacco products and their endogenous formation in consumers. *In*: I.K. O'Neill, R.C. von Borstel, C.T. Miller, J. Long and H. Bartsch (eds.), *N*-Nitroso compounds: Occurrence, biological effects and relevance to human cancer. Proceedings of the VIIIth International Symposium on *N*-Nitroso Compounds, held in Banff, Alberta, September 5–9, 1983. IARC Sci. Publ. 57 (ISBN 0-19-723055-5).

Hoffmann, D., J.D. Adams and K.D. Brunnemann. 1987. A critical look at *N*-nitrosamines in environmental tobacco smoke. Toxicol. Lett. 35: 1–8.

Howard, P.H., R.S. Boethling, W.F. Jarvis, W.M. Meylan and E.M. Michalenko (eds.). 1991. Handbook of environmental degradation rates. Lewis Publishers Inc., Chelsea, Michigan.

Howe, R.B. and K.S. Crump. 1982. Global82: A computer program to extrapolate quantal animal toxicity data to low doses. Science Research Systems, Ruston, Louisiana.

IARC (International Agency for Research on Cancer). 1978. Some *N*-nitroso compounds. IARC Monogr. Eval. Carcinog. Risk Chem. Hum. 17: 125–175.

Inui, N., Y. Nishi, M. Taketomi and M. Mori. 1979. Transplacental action of sodium nitrite on embryonic cells of Syrian golden hamster. Mutat. Res. 66: 149–158.

Ito, N., S. Fukushima, H. Tsuda and T. Shirai. 1982. Induction of preneoplastic and neoplastic lesions in rats treated with *N*-nitroso compounds. IARC Sci. Publ. 41: 597–601.

Jenkins, S.W.D., C.J. Koester, V. Taguchi, D.T. Wang, J.-P.F.P. Palmentier and K.P. Hong. 1995. *N*-Nitrosodimethylamine in drinking water using a rapid, solid-phase extraction method. Environ. Sci. Pollut. Res. Int. 2(4): 207–210.

Jobb, D.B., R.B. Hunsinger, O. Meresz and V.Y. Taguchi. 1993. A study of the occurrence and inhibition of formation of *N*-nitrosodimethylamine (NDMA) in the Ohsweken water supply. Proceedings of the 1992 Water Quality Technology Conference, American Water Works Association.

Johansson-Brittebo, E. and H. Tjälve. 1979. Studies on the distribution and metabolism of ^{14}C-dimethylnitrosamine in foetal and young mice. Acta Pharmacol. Toxicol. 45: 73–80.

Jorquera, R., A. Castonguay and H.M. Schuller. 1993. Effects of age and ethanol on DNA single-strand breaks and toxicity induced by 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone or *N*-nitrosodimethylamine in hamster and rat liver. Cancer Lett. 74: 175–181.

Kakizoe, T., T.-T. Wang, V.W.S. Eng, R. Furrer, P. Dion and W.R. Bruce. 1979. Volatile *N*-nitrosamines in the urine of normal donors and of bladder cancer patients. Cancer Res. 39: 829–832.

Kataoka, H., M. Kurisu and S. Shindoh. 1997. Determination of volatile *N*-nitrosamines in combustion smoke samples. Bull. Environ. Contam. Toxicol. 59: 570–576.

Kelly, P.M., J.I. Gray and J. Slattery. 1989. Direct "low-NOX" gas combustion heating of a spray drier during milk powder manufacture. J. Soc. Dairy Technol. 42(1): 14–18.

Khanna, S.D. and D. Puri. 1966. The hepatotoxic effects of dimethylnitrosamine in the rat. J. Pathol. Bacteriol. 91: 605–608 [cited in ATSDR, 1989].

Khudoley, V.V. 1977. The induction of tumours in *Rana temporaria* with nitrosamines. Neoplasma 24(3): 249–252.

Khudoley, V.V. and J.J. Picard. 1980. Liver and kidney tumours induced by *N*-nitrosodimethylamine in *Xenopus borealis* (Parker). Int. J. Cancer 25: 679–683.

Kimoto, W.I., C.J. Dooley, J. Carre and W. Fiddler. 1981. Nitrosamines in tap water after concentration by a carbonaceous adsorbent. Water Res. 15: 1099–1106.

Klein, R.G., I. Janowsky, B.L. Pool-Zobel, P. Schmezer, R. Hermann, F. Amelung, B. Spiegelhalder and W.J. Zeller. 1991. Effects of long-term inhalation of *N*-nitrosodimethylamine in rats. IARC Sci. Publ. 105: 322–328.

Klus, H., H. Begutter, G. Scherer, A.R. Tricker and F. Adlkofer. 1992. Tobacco-specific and volatile *N*-nitrosamines in environmental tobacco smoke of offices. Indoor Environ. 1: 348–350.

Kochany, J. 1999. Personal communication (letter dated July 30, 1999). Conestoga-Rovers & Associates, Waterloo, Ontario.

Kornbrust, D. and D. Dietz. 1985. Aroclor 1254 pretreatment effects on DNA repair in rat hepatocytes elicited by *in vivo* or *in vitro* exposure to various chemicals. Environ. Mutagen. 7: 857–870.

Krishna, G., M.L. Kropko and J.C. Theiss. 1990. Dimethylnitrosamine-induced micronucleus formation in mouse bone marrow and spleen. Mutat. Res. 242: 345–351.

Kunisaki, N., H. Matsuura and M. Hayashi. 1978. Absorption and decomposition of *N*-nitrosodimethylamine in rats. Shokuhin Eiseigaku Zasshi 19(1): 62–67 (in Japanese).

Laishes, B.A., D.J. Koropatnick and H.F. Stich. 1975. Organ-specific DNA damage induced in mice by the organotropic carcinogens 4-nitroquinoline-1-oxide and dimethylnitrosamine. Proc. Soc. Exp. Biol. Med. 149: 978–982.

Lakritz, L. and J.W. Pensabene. 1984. Survey of human milk for volatile *N*-nitrosamines and the influence of diet on their formation. Food Chem. Toxicol. 22: 721–724.

Lakritz, L., M.L. Simenhoff, S.R. Dunn and W. Fiddler. 1980. *N*-Nitrosodimethylamine in human blood. Food Cosmet. Toxicol. 18: 77–79.

Lakritz, L., R.A. Gates, A.M. Gugger and A.E. Wasserman. 1982. Nitrosamine levels in human blood, urine and gastric aspirate following ingestion of foods containing potential nitrosamine precursors or preformed nitrosamines. Food Chem. Toxicol. 20: 455–459.

Lawrence, G. 1999. Personal communication to B. Meek regarding nitrosamines in foods, July 21, 1999. Foods Directorate, Health Protection Branch, Health Canada, Ottawa, Ontario.

Lee, V.M., L.K. Keefer and M.C. Archer. 1996. An evaluation of the roles of metabolic denitrosation and α-hydroxylation in the hepatotoxicity of *N*-nitrosodimethylamine. Chem. Res. Toxicol. 9: 1319–1324.

Lijinsky, W. and M.D. Reuber. 1984. Carcinogenesis in rats by nitrosodimethylamine and other nitrosomethylalkylamines at low doses. Cancer Lett. 22: 83–88.

Lindamood, C., III, M.A. Bedell, K.C. Billings, M.C. Dyroff and J.A. Swenberg. 1984. Dose response for DNA alkylation, [^{3}H]thymidine uptake into DNA, and O^6-methylguanine-DNA methyltransferase activity in hepatocytes of rats and mice continuously exposed to dimethylnitrosamine. Cancer Res. 44: 196–200.

Loury, D.J., T. Smith-Oliver and B.E. Butterworth. 1987. Assessment of unscheduled and replicative DNA synthesis in rat kidney cells exposed *in vitro* or *in vivo* to unleaded gasoline. Fundam. Appl. Toxicol. 87: 127–140.

Mackay, D. 1991. Multimedia environmental models: the fugacity approach. Lewis Publishers Inc., Chelsea, Michigan.

Mackay, D. and S. Paterson. 1991. Evaluating the multimedia fate of organic chemicals: a level III fugacity model. Environ. Sci. Technol. 25: 427–436.

Magee, P.N. and J.M. Barnes. 1962. Induction of kidney tumours in the rat with dimethyl-nitrosamine (*N*-nitrosodimethylamine). J. Pathol. Bacteriol. 84: 19–31.

Mahanama, K.R.R. and J.M. Daisey. 1996. Volatile *N*-nitrosamines in environmental tobacco smoke: Analysis, emission factors, and indoor air exposures. Environ. Sci. Technol. 30: 1477–1484.

Mallik, M. and K. Tesfai. 1981. Transformation of nitrosamines in soil and *in vitro* by soil microoganisms. Bull. Environ. Contam. Toxicol. 27: 115–121.

Martino, P.E., M.I. Diaz Gomez, D. Tamayo, A.J. Lopez and J.A. Castro. 1988. Studies on the mechanism of the acute and carcinogenic effects of *N*-nitrosodimethylamine on mink liver. J. Toxicol. Environ. Health 23: 183–192.

Massey, R., M.J. Dennis, M. Pointer and P.E. Key. 1990. An investigation of the levels of *N*-nitrosodimethylamine, apparent total *N*-nitroso compounds and nitrate in beer. Food Addit. Contam. 7(5): 605–615.

McBean, E. 1999. Personal communication (e-mail sent May 30, 1999). Conestoga-Rovers & Associates, Waterloo, Ontario.

McLean, A.E.M. and P.N. Magee. 1970. Increased renal carcinogenesis by dimethyl nitrosamine in protein deficient rats. Br. J. Exp. Pathol. 51: 587–590.

Meek, M.E., R. Newhook, R. Liteplo and V. Armstrong. 1994. Approach to assessment of risk to human health for Priority Substances under the *Canadian Environmental Protection Act*. J. Environ. Sci. Health C12: 105–134.

Mehta, R., K.C. Silinskas, P.F. Zucker, A. Ronen, J.A. Heddle and M.C. Archer. 1987. Micronucleus formation induced in rat liver and esophagus by nitrosamines. Cancer Lett. 35: 313–320.

Ministers' Expert Advisory Panel. 1995. Report of the Ministers' Expert Advisory Panel on the second Priority Substances List under the *Canadian Environmental Protection Act* (CEPA). Ottawa, Ontario. 26 pp.

Mirsalis, J.C. and B.E. Butterworth. 1980. Detection of unscheduled DNA synthesis in hepatocytes isolated from rats treated with genotoxic agents: an *in vivo–in vitro* assay for potential carcinogens and mutagens. Carcinogenesis 1: 621–625.

Mirsalis, J.C., C.K. Tyson, K.L. Steinmetz, E.K. Loh, C.M. Hamilton, J.P. Bakke and J.W. Spalding. 1989. Measurement of unscheduled DNA synthesis and S-phase synthesis in rodent hepatocytes following *in vivo* treatment: testing of 24 compounds. Environ. Mol. Mutagen. 14: 155–164.

Mirsalis, J.C., G.S. Provost, C.D. Matthews, R.T. Hamner, J.E. Schindler, K.G. O'Loughlin, J.T. MacGregor and J.M. Short. 1993. Induction of hepatic mutations in *lacI* transgenic mice. Mutagenesis 8: 265–271.

Mizuishi, K., M. Teacake, H. Yamanobe, Y. Watanabe, Y. Unuma and Y. Yamanashi. 1987. Trace analysis of volatile *N*-nitrosamines in human milk. Kenkyu Nenpo Tokyo-toritsu Eisei Kenkyusho 38: 150–154 (in Japanese) [cited in Uibu *et al.*, 1996].

Moiseev, G.E. and V.V. Benemanskii. 1975. Concerning the carcinogenic activity of small concentrations of nitrosodimethylamine during inhalation. Vopr. Onkol. 21: 107–109 (translated for U.S. Environmental Protection Agency by Scitran [Scientific Translation Service], Santa Barbara, California).

Moore, G. 1999. Personal communication. Regulatory Affairs and Innovations Division, Pest Management Regulatory Agency, Health Canada.

Morrison, V. and J. Ashby. 1994. Reconciliation of five negative and four positive reports of the activity of dimethylnitrosamine in the mouse bone marrow micronucleus assay. Mutagenesis 9: 361–365.

Mumma, R.O., D.C. Raupach, J.P. Waldman, S.S.C. Tong, M.L. Jacobs, J.G. Babish, J.H. Hotchkiss, P.C. Wszolek, W.H. Gutenman, C.A. Bache and D.J. Lisk. 1984. National survey of elements and other constituents in municipal sewage sludges. Arch. Environ. Contam. Toxicol. 13: 75–83.

Nakatsuru, Y., S. Matsukama, N. Nemoto, H. Sugano, M. Sekiguchi and T. Ishikawa. 1993. O^6-Methylguanine-DNA methyltransferase protects against nitrosamine-induced hepatocarcinogenesis. Proc. Natl. Acad. Sci. U.S.A. 90: 6468–6472.

Napalkov, N.P. and V.A. Alexandrov. 1968. On the effects of blastomogenic substances during embryogenesis. Z. Krebsforsch. 71: 32–50 [cited in ATSDR, 1989].

Neal, S.B. and G.S. Probst. 1983. Chemically-induced sister-chromatid exchange *in vivo* in bone marrow of Chinese hamsters. An evaluation of 24 compounds. Mutat. Res. 113: 33–43.

Neft, R.E. and M.K. Conner. 1989. Induction of sister chromatid exchange in multiple murine tissues *in vivo* by various methylating agents. Teratogen. Carcinogen. Mutagen. 9: 219–237.

Nikaido, M.M., D. Dean-Raymond, A.J. Francis and M. Alexander. 1977. Recovery of nitrosamines from water. Water Res. 11: 1085–1087.

Nishie, K. 1983. Comparison of the effects of *N*-nitrosodimethylamine on pregnant and nonpregnant Holtzman rats. Food Chem. Toxicol. 21: 453–462.

Odagiri, Y., S. Adachi, H. Katayama and K. Takemoto. 1986. Detection of the cytogenetic effect of inhaled aerosols by the micronucleus test. Mutat. Res. 170: 79–83.

Oliver, J. 1979. Volatilization of some herbicide-related nitrosamines from soils. J. Environ. Qual. 8(4): 596–601.

OME (Ontario Ministry of the Environment). 1989. Information report on drinking water quality, Elmira, Ontario. Prepared by D. Ireland, Regional Operations Division, Cambridge, Ontario, November 14, 1989 (unpublished).

OME (Ontario Ministry of the Environment). 1990. Technical memorandum from A. Ng to G. De Brou dated April 27, 1990, regarding the Elmira (1990) survey: Results of the mobile TAGA. With covering memorandum dated May 5, 1990, from L. Lusis to E. Piché regarding the Elmira DMNA survey report, April 1990. Toronto, Ontario.

OME (Ontario Ministry of the Environment). 1991. Scientific criteria document for multimedia standard development No. 01-90. *N*-Nitrosodimethylamine. Hazardous Contaminants Coordination Branch, Toronto, Ontario. 64 pp.

OME (Ontario Ministry of the Environment). 1992a. Technical memorandum from A. Ng to M. Lusis dated July 24, 1992, regarding the Kitchener (1992) survey: NC Rubber Products Inc. — Results of the mobile TAGA 6000. With covering memorandum dated July 28, 1992, from M. Lusis to D. Ireland regarding the mobile TAGA 6000 survey of NC Rubber Products Inc. Toronto, Ontario.

OME (Ontario Ministry of the Environment). 1992b. Summary of water quality data. Canagagigue Creek, Elmira. Unpublished data prepared by the Technical Assessment Section, June 1992.

OME (Ontario Ministry of the Environment). 1994a. Removal of *N*-nitrosodimethylamine from the Ohsweken (Six Nations) water supply. Final report. Science and Technology Branch. Toronto, Ontario. November. 10 pp. + appendix (ISBN 0-7778-3439-1).

OME (Ontario Ministry of the Environment). 1994b. Windsor Air Quality Study: TAGA 6000 survey results. Prepared by A.C. Ng and N.S. Karellas. Windsor Air Quality Committee, Environmental Monitoring and Reporting Branch. Queen's Printer for Ontario. Fall 1994 (Publication No. PIBS 3152E; ISBN 0-7778-2831-6).

OME (Ontario Ministry of the Environment). 1994c. Memorandum — NDMA sanitary sewer discharge, unpublished data. Cambridge District Office. 3 pp.

OME (Ontario Ministry of the Environment). 1998a. Scientific criteria document for the development of an interim provincial water quality objective for *N*-nitrosodimethylamine (NDMA). Standards Development Branch, Toronto, Ontario. July. 28 pp.

OME (Ontario Ministry of the Environment). 1998b. Ontario drinking water surveillance program: 1990–July 1998 survey of Ontario water treatment plants. Unpublished data supplied by P. Lachmaniuk.

OMEE (Ontario Ministry of the Environment and Energy). 1996. Ontario drinking water surveillance program: 1994–1996 survey of Ontario water treatment plants. Unpublished data. Toronto, Ontario. 9 pp.

Opsal, R.B. and J.P. Reilly. 1986. Selective analysis of nitro- and nitroso-containing compounds by laser ionization gas chromatography/mass spectrometry. Anal. Chem. 58: 2919–2923.

Pancholy, S.K. 1978. Formation of carcinogenic nitrosamines in soils. Soil Biol. Biochem. 10: 27–32.

Parees, D.M. and S.R. Prescott. 1981. Direct determination of *N*-nitrosamines in amines using a gas chromatograph–thermal energy analyzer. J. Chromatogr. 205: 429–433.

Parsa, I., S. Friedman and C.M. Cleary. 1987. Visualization of O^6-methylguanine in target cell nuclei of dimethylnitrosamine-treated human pancreas by a murine monoclonal antibody. Carcinogenesis 8: 839–846.

Pedal, I., K. Besserer, K. Goerttler, B. Heymer, H.J. Mittmeyer, M. Oehmichen and D. Schmahl. 1982. Fatal nitrosamine poisoning. Arch. Toxicol. 50: 101–112 [cited in ATSDR, 1989].

Pegg, A.E. and W. Perry. 1981. Alkylation of nucleic acids and metabolism of small doses of dimethylnitrosamine in the rat. Cancer Res. 41: 3128–3132.

Peto, R., R. Gray, P. Brantom and P. Grasso. 1984. Nitrosamine carcinogenesis in 5120 rodents: chronic administration of sixteen different concentrations of NDEA, NDMA, NPYR and NPIP in the water of 4440 inbred rats, with parallel studies on NDEA alone of the effect of age of starting (3, 6 or 20 weeks) and of species (rats, mice or hamsters). *In*: I.K. O'Neill, R.C. von Borstel, C.T. Miller, J. Long and H. Bartsch (eds.), *N*-Nitroso compounds: Occurrence, biological effects and relevance to human cancer. Proceedings of the VIIIth International Symposium on *N*-Nitroso Compounds, held in Banff, Alberta, September 5–9, 1983. IARC Sci. Publ. 57: 627–665 (ISBN 0-19-723055-5).

Peto, R., R. Gray, P. Brantom and P. Grasso. 1991a. Effects on 4080 rats of chronic ingestion of *N*-nitrosodiethylamine or *N*-nitrosodimethylamine: a detailed dose–response study. Cancer Res. 51: 6415–6451.

Peto, R., R. Gray, P. Brantom and P. Grasso. 1991b. Dose and time relationships for tumor induction in the liver and esophagus of 4080 inbred rats by chronic ingestion of *N*-nitrosodiethylamine or *N*-nitrosodimethylamine. Cancer Res. 51: 6452–6469.

Petzold, G.L. and J.A. Swenberg. 1978. Detection of DNA damage induced *in vivo* following exposure of rats to carcinogens. Cancer Res. 38: 1589–1594.

Phillips, J.C., B.G. Lake, C.E. Heading, S.D. Gangolli and A.G. Lloyd. 1975. Studies on the metabolism of dimethylnitrosamine in the rat. I. Effects of dose, route of administration and sex. Food Cosmet. Toxicol. 13: 203–209.

Plomley, J.B., C.J. Koester and R.E. March. 1994. Determination of *N*-nitrosodimethylamine in complex environmental matrices by quadrupole ion storage tandem mass spectrometry enhanced by unidirectional ion ejection. Anal. Chem. 66: 4437–4443.

Pobel, D., E. Riboli, J. Cornée, B. Hémon and M. Guyader. 1995. Nitrosamine, nitrate and nitrite in relation to gastric cancer: A case–control study in Marseille, France. Eur. J. Epidemiol. 11: 67–73.

Pool, B.L., S.Y. Brendler, U.M. Liegibel, A. Tompa and P. Schmezer. 1990. Employment of adult mammalian primary cells in toxicology: *in vivo* and *in vitro* genotoxic effects of environmentally significant *N*-nitrosodialkylamines in cells of the liver, lung, and kidney. Environ. Mol. Mutagen. 15: 24–35.

Risch, H.A., M. Jain, N.W. Choi, J.G. Fodor, C.J. Pfeiffer, G.R. Howe, L.W. Harrison, K.J.P. Craib and A.B. Miller. 1985. Dietary factors and the incidence of cancer of the stomach. Am. J. Epidemiol. 122: 947–957.

Robbiano, L., E. Mereto, A.M. Morando, P. Pastore and G. Brambilla. 1997. An *in vivo* micronucleus assay for detecting the clastogenic effect in rat kidney cells. Mutat. Res. 390: 51–57.

Rogers, M.A.M., T.L. Vaughan, S. Davis and D.B. Thomas. 1995. Consumption of nitrate, nitrite, and nitrosodimethylamine and the risk of upper aerodigestive tract cancer. Cancer Epidemiol. Biomarkers Prev. 4: 29–36.

Salminen, J. 1999. Priority Substances assessment on NDMA. Internal memorandum dated September 13, 1999, from A/Chief, Chemical Health Hazard Assessment Division, Bureau of Chemical Safety, Food Directorate, to B. Meek, Head, Priority Substances Section, Bureau of Chemical Hazards, Environmental Health Directorate, Health Canada, Ottawa, Ontario (File No. FP99072001-597).

Sato, S., M. Taketomi and T. Morita. 1992. Simplified mouse peripheral reticulocyte micronucleus test with dimethylnitrosamine. Mutat. Res. 278: 103–107.

Sawada, S., T. Yamanaka, K. Yamatsu, C. Furihata and T. Matsushima. 1991. Chromosome aberrations, micronuclei and sister-chromatid exchanges (SCEs) in rat liver induced *in vivo* by hepatocarcinogens including heterocyclic amines. Mutat. Res. 251: 59–69.

Sax, N. and R. Lewis, Sr. 1987. Hawley's condensed chemical dictionary. 11th edition. Van Nostrand Reinhold Co., New York, N.Y. p. 832.

Scanlan, R.A., J.F. Barbour, F.W. Bodyfelt and L.M. Libbey. 1994. *N*-Nitrosodimethylamine in nonfat dry milk. *In*: R.N. Loeppky and C.J. Michejda (eds.), Proceedings of the 204th National Meeting of the American Chemical Society on Nitrosamines and Related *N*-Nitroso Compounds, August 23–28, 1992, Washington, D.C. pp. 34–41 (ACS Symposium Series 553).

Schmidt, J.D. and G.P. Murphy. 1966. Urinary lactic dehydrogenase activity in rats with dimethylnitrosamine induced renal tumors. Invest. Urol. 4: 57–63.

Sen, N.P. 1986. Formation and occurrence of nitrosamines in food. *In*: L.A. Cohen and B.S. Reddy (eds.), Diet, nutrition and cancer: A critical evaluation. Vol. II: Micro nutrients, nonnutritive dietary factors, and cancer. CRC Press, Boca Raton, Florida. pp. 135–160.

Sen, N.P. and S. Seaman. 1981a. Gas–liquid chromatographic–thermal energy analyzer determination of *N*-nitrosodimethylamine in beer at low parts per billion level. J. Assoc. Off. Anal. Chem. 64: 933–938.

Sen, N.P. and S. Seaman. 1981b. Volatile *N*-nitrosamines in dried foods. J. Assoc. Off. Anal. Chem. 64(5): 1238–1242.

Sen, N.P., B.A. Donaldson, S. Seaman, J.R. Iyengar and W.F. Miles. 1978. Recent studies in Canada on the analysis and occurrence of volatile and non-volatile *N*-nitroso compounds in foods. IARC Sci. Publ. 19: 373–393.

Sen, N.P., S. Seaman and W.F. Miles. 1979. Volatile nitrosamines in various cured meat products: Effect of cooking and recent trends. Agric. Food Chem. 27(6): 1354–1357.

Sen, N.P., S. Seaman and M. McPherson. 1980a. Nitrosamines in alcoholic beverages. J. Food Saf. 2: 13–18.

Sen, N.P., S. Seaman and M. McPherson. 1980b. Further studies on the occurrence of volatile and non-volatile nitrosamines in foods. *In*: A. Walker, L. Griciute, M. Castegnaro and M. Borzsonyi (eds.), *N*-Nitroso compounds: Analysis, formation and occurrence. IARC Sci. Publ. 31: 457–465.

Sen, N.P., S. Seaman, S. Clarkson, F. Garrod and P. Lalonde. 1984. Volatile *N*-nitrosamines in baby bottle rubber nipples and pacifiers. Analysis, occurrence and migration. *In*: I.K. O'Neill, R.C. von Borstel, C.T. Miller, J. Long and H. Bartsch (eds.), *N*-Nitroso compounds: Occurrence, biological effects and relevance to human cancer. Proceedings of the VIIIth International Symposium on *N*-Nitroso Compounds, held in Banff, Alberta, September 5–9, 1983. IARC Sci. Publ. 57: 51–57 (ISBN 0-19-723055-5).

Sen, N.P., L. Tessier, S.W. Seaman and P.A. Baddoo. 1985. Volatile and nonvolatile nitrosamines in fish and the effect of deliberate nitrosation under simulated gastric conditions. J. Agric. Food Chem. 33: 264–268.

Sen, N.P., P.A. Baddoo, D. Weber and M. Boyle. 1994. A sensitive and specific method for the determination of *N*-nitrosodimethylamine in drinking water and fruit drinks. Int. J. Environ. Anal. Chem. 56: 149–163.

Sen, N.P., S.W. Seaman, C. Bergeron and R. Brousseau. 1996. Trends in the levels of *N*-nitrosodimethylamine in Canadian and imported beers. J. Agric. Food Chem. 44(6): 1498–1501.

Shu, L. and P.F. Hollenberg. 1996. Role of cytochrome P450 in DNA damage induced by *N*-nitrosodialkylamines in cultured rat hepatocytes. Carcinogenesis 17: 569–576.

Shu, L. and P.F. Hollenberg. 1997. Alkylation of cellular macromolecules and target specificity of carcinogenic nitrosodialkylamines: metabolic activation by cytochromes P450 2B1 and 2E1. Carcinogenesis 18(4): 801–810.

Smith, J. 1999. Personal communication (e-mail dated November 10, 1999). Regulatory Affairs and Innovations Division, Pest Management Regulatory Agency, Health Canada.

Souliotis, V.L., S. Chhabra, L.M. Anderson and S.A. Kyrtopoulos. 1995. Dosimetry of *O*⁶-methylguanine in rat DNA after low-dose, chronic exposure to *N*-nitrosodimethylamine (NDMA). Implications for the mechanism of NDMA hepatocarcinogenesis. Carcinogenesis 16: 2381–2387.

Spiegelhalder, B. and R. Preussmann. 1984. Contamination of toiletries and cosmetic products with volatile and nonvolatile *N*-nitroso carcinogens. J. Cancer Res. Clin. Oncol. 108: 160–163.

Spiegelhalder, B., G. Eisenbrand and R. Preussmann. 1980. Occurrence of volatile nitrosamines in food: A survey of the West German market. *In*: A. Walker, L. Griciute, M. Castegnaro and M. Borzsonyi (eds.), *N*-Nitroso compounds: Analysis, formation and occurrence. IARC Sci. Publ. 31: 467–479.

Stehlik, G., O. Richter and H. Altmann. 1982. Concentration of dimethylnitrosamine in the air of smoke-filled rooms. Ecotoxicol. Environ. Saf. 6: 495–500.

Swann, P.F., A.M. Coe and R. Mace. 1984. Ethanol and dimethylnitrosamine and diethylnitrosamine metabolism and disposition in the rat. Possible relevance to the influence of ethanol on human cancer incidence. Carcinogenesis 5(10): 1337–1343.

Swenberg, J.A., D.G. Hoel and P.N. Magee. 1991. Mechanistic and statistical insight into the large carcinogenesis bioassays on *N*-nitrosodiethylamine and *N*-nitrosodimethylamine. Cancer Res. 51: 6409–6414.

Taguchi, V.Y. 1998. Personal communication. Laboratory Services Branch, Ontario Ministry of the Environment.

Taguchi, V.Y., S.W.D. Jenkins, D.T. Wang, J.-P.F.P. Palmentier and E.J. Reiner. 1994. Determination of *N*-nitrosodimethylamine by isotope dilution, high-resolution mass spectrometry. Can. J. Appl. Spectrosc. 39: 87–93.

Tanaka, A., A. Hisanaga, T. Inamasu, M. Hirata and N. Ishinishi. 1988. A comparison of the carcinogenicity of *N*-nitrosodiethylamine and *N*-nitrosodimethylamine after intratracheal instillation into Syrian golden hamsters. Food Chem. Toxicol. 26: 847–850.

Tate, R.L., III and M. Alexander. 1975. Stability of nitrosamines in samples of lake water, soil, and sewage. J. Natl. Cancer Inst. 54: 327–330.

Tates, A.D., I. Neuteboom, M. Hofker and L. den Engelse. 1980. A micronucleus technique for detecting clastogenic effects of mutagens/carcinogens (DEN, DMN) in hepatocytes of rat liver *in vivo*. Mutat. Res. 74: 11–20.

Tates, A.D., I. Neuteboom, N. de Vogel and L. den Engelse. 1983. The induction of chromosomal damage in rat hepatocytes and lymphocytes. I. Time-dependent changes of the clastogenic effects of diethylnitrosamine, dimethylnitrosamine and ethyl methanesulfonate. Mutat. Res. 107: 131–151.

Tates, A.D., I. Neuteboom, A.H.M. Rotteveel, N. de Vogel, G.J. Menkveld and L. den Engelse. 1986. Persistence of preclastogenic damage in hepatocytes of rats exposed to ethylnitrosourea, diethylnitrosamine, dimethylnitrosamine and methyl methanesulfonate. Correlation with DNA *O*-alkylation. Carcinogenesis 7: 1053–1058.

Terao, K., T. Aikawa and K. Kera. 1978. A synergistic effect of nitrosodimethylamine on sterigmatocystin carcinogenesis in rats. Food Cosmet. Toxicol. 16: 591–596.

Terracini, B., G. Palestro, M.R. Gigliardi and R. Montesano. 1966. Carcinogenicity of dimethylnitrosamine in Swiss mice. Br. J. Cancer 20: 871–876.

Thomas, R.G. 1982. Volatilization from water. *In*: W.J. Lyman, W.F. Reehl and D.H. Rosenblatt (eds.), Handbook of chemical property estimation methods. McGraw-Hill, New York, N.Y. pp. 15–27.

Tinwell, H, P.A. Lefevre and J. Ashby. 1994. Mutation studies with dimethyl nitrosoamine in young and old *lac I* transgenic mice. Mutat. Res. 307: 501–508.

Tomkins, B.A. and W.H. Griest. 1996. Determinations of *N*-nitrosodimethylamine at part-per-trillion concentrations in contaminated groundwaters and drinking waters featuring carbon-based membrane extraction disks. Anal. Chem. 68: 2533–2540.

Tomkins, B.A., W.H. Griest and C.E. Higgins. 1995. Determination of *N*-nitrosodimethylamine at part-per-trillion levels in drinking waters and contaminated groundwaters. Anal. Chem. 67: 4387–4395.

Tricker, A.R. and R. Preussmann. 1992. Volatile *N*-nitrosamines in mainstream cigarette smoke: occurrence and formation. Clin. Invest. 70: 283–289.

Tricker, A.R., B. Pfundstein, E. Theobald, R. Preussmann and B. Spiegelhalder. 1991a. Mean daily intake of volatile *N*-nitrosamines from foods and beverages in West Germany in 1989–1990. Food Chem. Toxicol. 29(11): 729–732.

Tricker, A.R., C. Ditrich and R. Preussmann. 1991b. *N*-Nitroso compounds in cigarette tobacco and their occurrence in the mainstream tobacco smoke. Carcinogenesis 12(2): 257–261.

Tsutsumi, M., Y. Matsuda and A. Takada. 1993. Role of ethanol-inducible cytochrome P-450 2E1 in the development of hepatocellular carcinoma by the chemical carcinogen, *N*-nitrosodimethylamine. Hepatology 18: 1483–1489.

Uibu, J., O. Tauts, A. Levin, N. Shimanovskaya and R. Matto. 1996. *N*-Nitrosodimethylamine, nitrate and nitrate-reducing microorganisms in human milk. Acta Paediatr. 85: 1140–1142.

U.K. MAFF (United Kingdom Ministry of Agriculture, Fisheries and Food). 1992. Nitrate, nitrite and *N*-nitroso compounds in foods — Second report. The 32nd Report of the Steering Group on Chemical Aspects of Food Surveillance. HMSO, London, U.K. 77 pp. (Food Surveillance Paper No. 32l; ISSN 0141-8521).

U.S. EPA (United States Environmental Protection Agency). 1984. EPA Method Study 17, Method 607 (Nitrosamines). Quality Assurance Branch, Environmental Monitoring and Support Laboratory, Cincinnati, Ohio (EPA-600/4-84-051; PB84207646).

Vermeer, I.T.M., D.M.F.A. Pachen, J.W. Dallinga, J.C.S. Kleinjans and J.M.S. van Maanen. 1998. Volatile *N*-nitrosamine formation after intake of nitrate at the ADI level in combination with an amine-rich diet. Environ. Health Perspect. 106(8): 459–463.

Volmer, D.A., J.O. Lay, Jr., S.M. Billedeau and D.L. Vollmer. 1996. Detection and confirmation of *N*-nitrosodialkylamines using liquid chromatography–electrospray ionization coupled on-line with a photolysis reactor. Anal. Chem. 68: 546–552.

Von Rappard, E., G. Eisenbrand and R. Preussmann. 1976. Selective detection of *N*-nitrosamines by gas chromatography using a modified microelectrolytic conductivity detector in the pyrolytic mode. J. Chromatogr. 124: 247–255.

Wang, X., T. Suzuki, T. Itoh, M. Honma, A. Nishikawa, F. Furukawa, M. Takahashi, M. Hayashi, T. Kato and T. Sofuni. 1998. Specific mutational spectrum of dimethylnitrosamine in the *lacI* transgene of Big Blue® C57BL/6 mice. Mutagenesis 13: 625–630.

Webb, K.S., T.A. Gough, A. Carrick and D. Hazelby. 1979. Mass spectrometric and chemiluminescent detection of picogram amounts of *N*-nitrosodimethylamine. Anal. Chem. 51: 989–992.

Webb, K.S., B.J. Wood and T.A. Gough. 1983. The effect of the intake of a nitrosatable drug on the nitrosamine levels in human urine. J. Anal. Toxicol. 7: 181–184.

Webster, R.P., M.D. Gawde and R.K. Bhattacharya. 1996. Protective effect of rutin, a flavonol glycoside, on the carcinogen-induced DNA damage and repair enzymes in rats. Cancer Lett. 109: 185–191.

Wild, D. 1978. Cytogenetic effects in the mouse of 17 chemical mutagens and carcinogens evaluated by the micronucleus test. Mutat. Res. 56: 319–327.

Wright, S. 1999. Personal communication (e-mail dated July 15, 1999, regarding Product Safety Laboratory Method C-24 for determining nitrosamines in pacifiers and bottle nipples and cyclical enforcement policy). Product Safety Laboratory, Product Safety Bureau, Health Protection Branch, Health Canada, Ottawa, Ontario.

Yamamoto, M., T. Yamada and A. Tanimura. 1980. Volatile nitrosamines in human blood before and after ingestion of a meal containing high concentrations of nitrate and secondary amines. Food Cosmet. Toxicol. 18: 297–299.

Yang, C.S., H. Ishizaki, M. Lee, D. Wade and A. Fadel. 1991. Deuterium isotope effect in the interaction of *N*-nitrosodimethylamine, ethanol, and related compounds with cytochrome P-450IIE1. Chem. Res. Toxicol. 4: 408–413.

APPENDIX A SEARCH STRATEGIES EMPLOYED FOR IDENTIFICATION OF RELEVANT DATA

Environmental assessment

Data relevant to the assessment of whether NDMA is "toxic" to the environment under CEPA were identified from existing review documents, published reference texts and on-line searches conducted between January and April, 1996, of the following databases: Aqualine (1984–1996), ASFA (Aquatic Sciences and Fisheries Abstracts, Cambridge Scientific Abstracts; 1984–1996), BIOSIS (Biosciences Information Services; 1984–1996), CAB (Commonwealth Agriculture Bureaux; 1984–1996), CESARS (Chemical Evaluation Search and Retrieval System, Ontario Ministry of the Environment and Michigan Department of Natural Resources; 1996), Chemical Abstracts (1984–1996), CHRIS (Chemical Hazard Release Information System; 1996), Current Contents (1993–January 15, 1996), ELIAS (Environmental Library Integrated Automated System, Environment Canada library; 1990–February 1996), Enviroline (R.R. Bowker Publishing Co.; 1984–1996), Environmental Abstracts (1975–February 1996), Environmental Bibliography (Environmental Studies Institute, International Academy at Santa Barbara; 1984–1996), GEOREF (Geo Reference Information System, American Geological Institute; 1984–1996), HSDB (Hazardous Substances Data Bank, U.S. National Library of Medicine; 1984–1996), Life Sciences (Cambridge Scientific Abstracts; 1984–1996), NTIS (National Technical Information Service, U.S. Department of Commerce; 1984–1996), Pollution Abstracts (Cambridge Scientific Abstracts, U.S. National Library of Medicine; 1984–1996), POLTOX (Cambridge Scientific Abstracts, U.S. National Library of Medicine; 1990–1995), RTECS (Registry of Toxic Effects of Chemical Substances, U.S. National Institute for Occupational Safety and Health; 1996), Toxline (U.S. National Library of Medicine; 1984–1996), TRI87–94 (Toxic Chemical Release Inventory, U.S. Environmental Protection Agency, Office of Toxic Substances; 1993), USEPA-ASTER (Assessment Tools for the Evaluation of Risk, U.S. Environmental Protection Agency; up to December 21, 1994), WASTEINFO (Waste Management Information Bureau of the American Energy Agency; 1973–September 1995), Water Resources Abstracts (U.S. Geological Survey, U.S. Department of the Interior; 1984–1996).

A survey of Canadian industry was carried out under authority of Section 16 of CEPA (Environment Canada, 1997c). Companies were required to provide information on uses, releases, environmental concentrations, effects or other data on NDMA available to them if they met the trigger quantity of 10 g NDMA per year. Reveal Alert was used to maintain an ongoing record of the current scientific literature pertaining to the potential environmental effects of NDMA. Data obtained after August 31, 1998, were not considered in this assessment unless they were critical data received during the 60-day public review of the report (February 19 to April 19, 2000).

Health assessment

Data relevant to the assessment of the potential risks of NDMA to human health were identified through evaluation of existing review documents of the U.S. Agency for Toxic Substances and Disease Registry (ATSDR, 1989), the International Agency for Research on Cancer (IARC, 1978) and the Ontario Ministry of the Environment (OME, 1991), as well as reviews prepared under contract by BIBRA Toxicology

International (1997, 1998). To identify additional relevant toxicological data, literature searches on NDMA were conducted using the strategy of searching by its name or CAS registry number in the following databases: CCRIS (Chemical Carcinogenesis Research Information System, U.S. National Cancer Institute), Dialogue, EMIC (Environmental Mutagen Information Center database, Oak Ridge National Laboratory) and EMICBACK (backfile of EMIC), ETICBACK (backfile of Environmental Teratology Information Center database, U.S. Environmental Protection Agency and U.S. National Institute of Environmental Health Sciences), GENETOX (Genetic Toxicology, Office of Toxic Substances, U.S. Environmental Protection Agency), HSDB, IRIS (Integrated Risk Information System, U.S. Environmental Protection Agency) and RTECS. Its name, registry number and major synonyms were searched in the ToxlinePlus (1985–1999) and Toxline (before 1985) databases. The CAS registry number was searched in the Toxlit (1981–1999) database. The EMBASE database, for 1981–1999, was searched using the name, registry number and major synonyms, combined with a link to toxicological information. In addition to the above sources of information, numerous provincial and federal government officials and representatives of various industrial sectors were contacted between February and August of 1996 for data relevant to exposure and/or effects.